STUDIES IN THE CARBAZOLE SERIES

by

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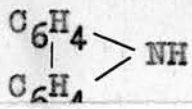
INTRODUCTION.

Carbazole was discovered in 1872 by Graebe and Glaser (1) while investigating a method for the purification of anthracene. After distillation of crude anthracene a residue remained which with hot 50% caustic potash yielded a potassium compound. Treatment of this with water gave an insoluble residue. By sublimation Graebe and Glaser obtained from the residue glistening white plates, melting at 238°C, and boiling at 338°C, and after analysis assigned the empirical formula $C_{12}H_9N$. Since the substance had in general the properties of a hydrocarbon, yet contained nitrogen, they named it 'Carbazole'.

Braun and Greiff (2) obtained a similar compound by the distillation of "commercial anilines" with lime, while Graebe later showed that carbazole could be prepared by the pyrolysis of aniline or diphenylamine (3, 4), and suggested the structure:-



ERRATA

Page 19, Line 4. Instead of "11-hydroxy-9-benzoyl-1:2:3:11-tetrahydrocarbazole" read "11-hydroxy-9-benzoyl-2:3:4:11-tetrahydrocarbazole".

Page 106, Heading. Interline the word "tetrahydrocarbazole" between "1-ketotetrahydrocarbazole" and "and".

anthracene, containing about 22% carbazole. This may be isolated by conversion to its potassium derivative with solid caustic potash, and subsequent decomposition with water. Carbazole can be separated satisfactorily from anthracene hydrocarbons by extraction of the former with crude pyridine bases, or the latter with carbon tetrachloride (5).

The catalytic hydrogenation of tar fractions at high temperatures and pressures gives a product from which carbazole may be isolated by vacuum distillation, followed by crystallisation of the crude condensate. A molybdenum-chromium-manganese catalyst (6) or one composed of alkali or alkaline earth metals, or their hydrides, may be used for this purpose (7).

Commercial samples of carbazole may be purified by extracting accompanying phenanthrene with solvent naphthas, sulphonation of anthracene with cold 98% sulphuric acid, and sublimation of the residual carbazole (8).

Crystallised from alcohol, glacial acetic acid, benzene or toluene, carbazole separates out in the form of glistening plates or flakes, but it is very difficult to obtain in the pure state, and various melting points have been quoted in the literature. The sample first obtained by Graebe and Glaser/

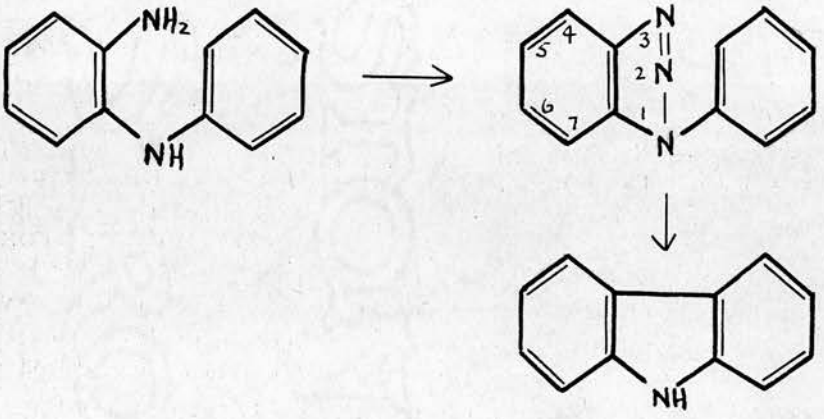
Glaser melted at 238°C, but more recent workers have shown it to be in the neighbourhood of 245°C. The most reliable melting points quoted are probably those of Senseman and Nelson (9), 244.8°C; Tucker (10), 245°C; Zelinsky, Titz and Gaverdowskaja (11), 245·6°C; Aristov (12), 246°C; and Kirby (13), 247°C. It is an extremely stable compound, distilling unchanged over glowing zinc dust (1), and is only weakly basic, dissolving in cold concentrated sulphuric acid from which it is precipitated on dilution with water.

Several colour tests are used for the detection of carbazoles, the commonest being treatment with concentrated sulphuric acid and a drop of nitric acid, which generally produces a deep blue-green colour. Carbazole and many substituted carbazoles were found by McLean and Campbell (14) to give a dark green colour on treatment with Mecke's reagent (a mixture of selenious acid and concentrated sulphuric acid), but the test is not specific for carbazoles.

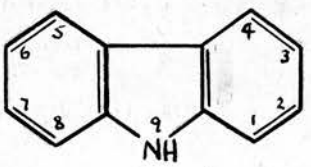
When the vapour of an alcoholic solution of carbazole is brought into contact with a pine splint soaked in hydrochloric acid, a red colour is produced, since carbazole is an indole derivative.

Syntheses of Carbazole and Derivatives:

Graebe and Ullmann (15) in 1896 synthesised carbazole by the distillation of phenylazimidobenzene (1-phenyl-1:2:3-benztriazole), prepared by the action of nitrous acid on ortho-aminodiphenylamine. When heated at 360°, nitrogen is evolved, carbazole distilling over almost free from the triazole. Ullmann (16, 17) later applied this method to the synthesis of many derivatives of carbazole, including 1- and 3-methylcarbazole; 1:3-dimethyl; 2- and 3-chloro; 3-amino; 1:2-naphtho and 1:2-naphtho-3-methylcarbazole.



The usual nomenclature of carbazole derivatives, that adopted by Ullmann, corresponds to the following scheme:-

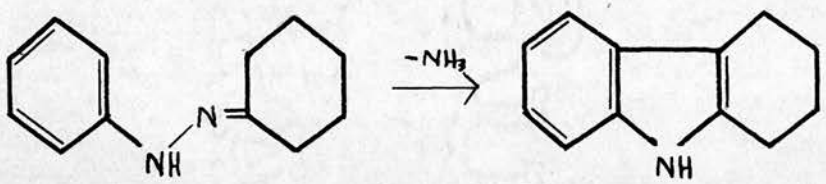


Many/

Many attempts were later made to synthesise by this method carbazoles containing unsaturated groups, but they met with no success until, in 1942, Preston, Tucker and Cameron (18) reported the synthesis of carbazoles containing nitro, cyano and acetyl groupings. 3-Nitrocarbazole was obtained only as a trace from 5-nitro-1-phenylbenztriazole, but an 18% yield of 1-nitrocarbazole was obtained on heating 7-nitro-1-phenylbenztriazole with copper bronze over a free flame, followed by extraction with benzene. 3-Acetylcarbazole (22%) and 3-cyanocarbazole (34% yield) were also prepared thus. There are, however, certain limitations to the method. Bremer (19) prepared certain aminotriazoles and attempted their conversion to carbazole derivatives. 5-Amino-1-p-tolyl-1:2:3-benztriazole and 5-amino-1-(p-aminophenyl)-1:2:3-benztriazole were successfully converted to 3-amino-6-methylcarbazole and 3:6-diaminocarbazole (trace). Other aminotriazoles which he prepared underwent decomposition on heating. In 1941 Campbell and McLean (14) reported that when 7-bromo-1-phenylbenztriazole-5-carboxylic acid was heated at 360°C with quicklime, carbazole, and not the expected 1-bromocarbazole, was obtained.

Dreschel (20) and Baeyer (21, 22) made a discovery which was to lead to a new synthesis of carbazole/

carbazole derivatives. The phenylhydrazone of cyclohexanone, when warmed with dilute mineral acids, yielded only small amounts of phenylhydrazine and cyclohexanone, being almost entirely converted by loss of ammonia into tetrahydrocarbazole (analogous to the Fischer Synthesis of indole derivatives).



Borsche (23) investigated the reaction more fully, showing that many substituted tetrahydrocarbazoles could be obtained, including alkyl, halogeno and nitro derivatives, and it is usually termed the "Borsche Synthesis". Reduction of these derivatives with tin and hydrochloric acid gave the corresponding hexahydrocarbazoles, while, in the case of those tetrahydrocarbazoles which were volatile, distillation over finely divided lead oxide (heated) yielded the carbazole. Since a great variety of tetrahydrocarbazoles could be synthesised by Borsche's method, the question of dehydrogenation to carbazole derivatives was important. Obviously distillation over lead oxide could not be applied in the case of nitro and halogeno-tetrahydrocarbazoles.

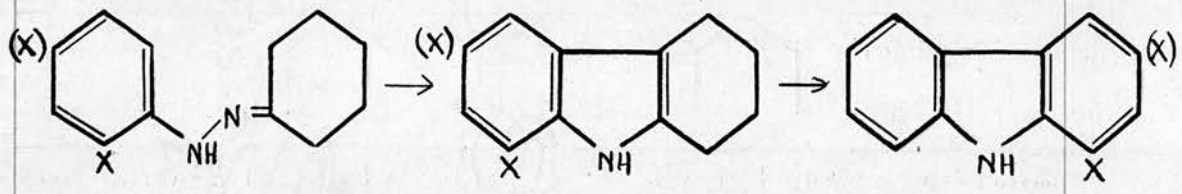
Perkin and Plant (24) after the unsuccessful use of permanganate, found mercuric acetate suitable/

suitable for the preparation of carbazole and 9-methylcarbazole, but evidently did not find it of general applicability for they later (25) used sulphur as a dehydrogenating agent, obtaining yields of 15% to 30%. Dehydrogenation of 6-nitrotetrahydrocarbazole with sulphur was, however, unsuccessful. Cooke and Gulland (26) obtained a 91% yield of carbazole on boiling together tetrahydrocarbazole and 2% aqueous palladous chloride. Only very small quantities of material were used, however, and the method would probably not be effective on a much larger scale. Chloranil was found by Barclay and Campbell (27) to have an extremely wide application as a dehydrogenating agent, giving very good yields of carbazole derivatives, and several new substituted carbazoles were prepared from the corresponding tetrahydrocarbazoles by this method. The dehydrogenation of alkyl tetrahydrocarbazoles with a 5% palladium-charcoal catalyst, also in very good yield, has been described by Horning, Horning and Walker (28).

Useful modifications of Borsche's method include boiling the phenylhydrazone with glacial acetic instead of mineral acid (24) to effect ring-closure, giving cleaner products, and a one-stage process (phenylhydrazine to tetrahydrocarbazole) described by Rogers and Corson (29). In the latter method/

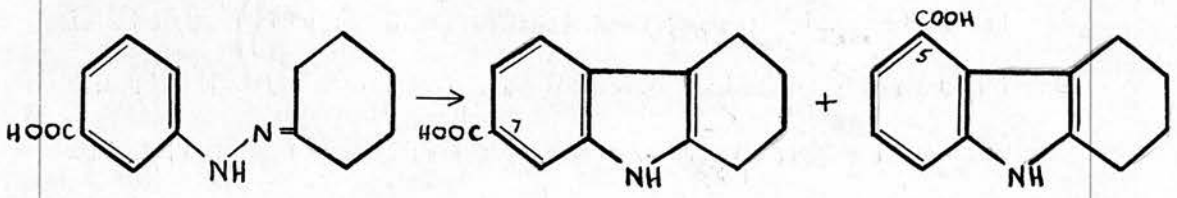
method the condensation of the appropriate phenylhydrazine with cyclohexanone is carried out in glacial acetic acid solution or in the presence of mineral acid, and ring-closure also takes place.

Borsche's Synthesis, used to prepare many new carbazole derivatives, has also proved very useful in the orientation of existing carbazoles and tetrahydrocarbazoles. If the synthesis is carried out with o- or p-substituted amines, the structure of the tetrahydrocarbazole produced is immediately known:



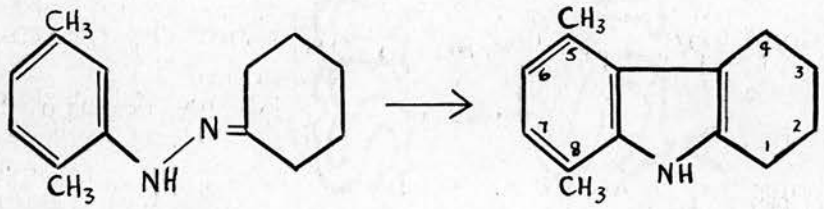
Compounds prepared in this fashion can then be compared with those obtained by direct substitution.

With m-substituted amines, however, two products are theoretically possible. Thus m-hydrazinobenzoic acid yields a mixture of tetrahydrocarbazole-5- and 7-carboxylic acids (30).



This synthesis has been employed in the preparation of several alkyl derivatives of tetrahydrocarbazole/

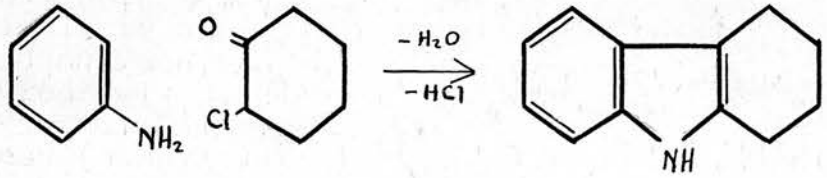
tetrahydrocarbazole, but no account can be found in the literature of the synthesis of dimethyltetrahydrocarbazoles with both methyl groups in the unreduced ring. Their preparation would involve the condensation of cyclohexanone with appropriate xylylhydrazines, most of which are unstable substances decomposing in light and air (31, 32, 33, 34).



CYCLOHEXANONE - p- XYLYLHYDRAZONE 5:8 - DIMETHYLTETRAHYDROCARBAZOLE

Borsche, however, condensed 3-methylcyclohexanone and m-4-xylylhydrazine, and from the hydrazone obtained 2:5:8-trimethyltetrahydrocarbazole, but he gave no experimental details (23).

A synthesis of tetrahydrocarbazole and methyltetrahydrocarbazoles, described in a German patent (35), involved the condensation of aromatic amines with 2-chlorocyclohexanone.



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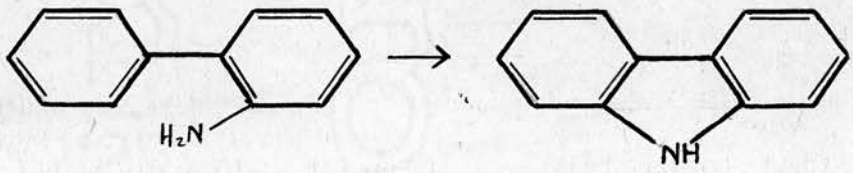
This method has been further studied by McCall (36), who has successfully prepared alkyl, carbethoxy and halogeno tetrahydrocarbazoles. If further substituted chlorocyclohexanones are used, however, complications arise.

Other syntheses of carbazole exist, several of which have derivatives of diphenyl as starting materials. Blank's method of preparing carbazole by pyrolysis of 2-aminodiphenyl (o-xenylamine) at very high temperatures (37) has been repeated by Morgan and Walls who have also carried out the oxidation catalytically at much lower temperatures (450-500°C) (38). Good yields of very pure carbazole were obtained.



Tauber (39) found that by heating 2:2'-diaminodiphenyl with 25% sulphuric acid or 15% hydrochloric acid at 200°C, or alternatively (40) by the reduction with potassium hydrosulphide of the tetrazo solution prepared from 2:2-diaminodiphenyl, a good yield of carbazole could be obtained.

Other syntheses of carbazole have been reported, but are not of preparative value.

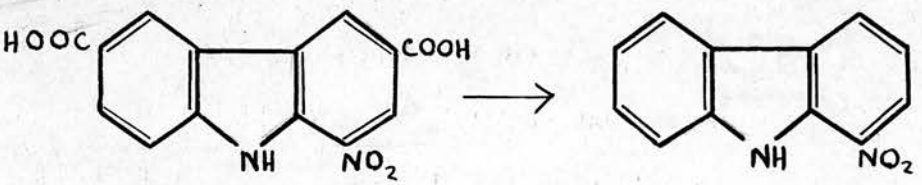
Substitution:

Substitution in the N position: Carbazole reacts with methyl magnesium iodide to give N-carbazole magnesium iodide, and with KOH (fusion) to give potassium carbazole. N-alkyl, -aryl and -acyl derivatives may be prepared by treating these two compounds or carbazole itself with the appropriate reagent. Boeseken (41) acetylated carbazole with acetic anhydride in the presence of a trace of sulphuric acid or ferric chloride at 98°C. A great advance was made, however, when Stevens and Tucker(42) obtained N-alkyl and -acyl derivatives in almost quantitative yield by the action at room temperature of aqueous alkali on carbazole or its derivatives in alcohol or acetone solution, and in the presence of the appropriate alkylating or acylating agent. The method has a very wide application, though it is capricious.

Potassium carbazole is a useful substance for the preparation of carbazole carboxylic acids by the action of carbon dioxide at high temperatures and under pressure. Various mono- and di-carboxylic acids are formed according to the temperature and length of heating.

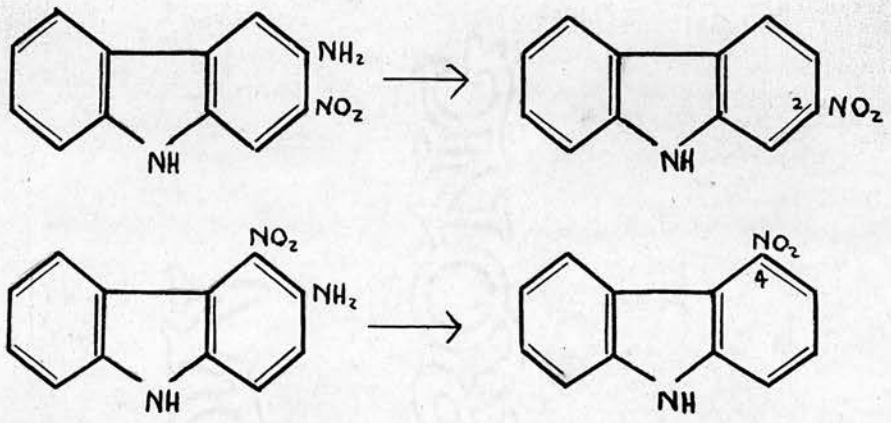
General substitution: Certain substituted carbazoles can be obtained by direct sulphonation, bromination/

bromination, nitration, etc. in a similar fashion to the benzene series, but a mixture of products often results. The 3- and 6-, followed by 1- and 8- positions, are the most reactive. Thus limited nitration of carbazole produces mainly 3-nitrocarbazole, with a little 1-nitrocarbazole, while complete nitration yields 1:3:6:8-tetranitrocarbazole. Direct substitution is usually employed to prepare 3- substituted carbazoles, but where a separation is practicable 1- substituted derivatives are also made by this method. Tucker and co-workers, for example, obtained 1-nitrocarbazole by chromatographic separation of 1- and 3-nitrocarbazole, but in very small yield. Other mono-substituted carbazoles may be produced by the removal of groups from poly-substituted derivatives. Preston, Tucker and Cameron prepared 1-nitrocarbazole by nitration of 3:6-carbazoledicarboxylic acid, followed by decarboxylation (18),



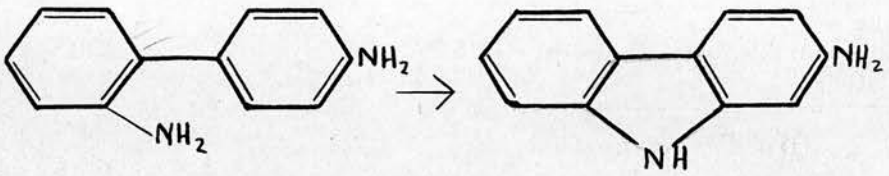
while a British patent (43) describes a method of preparing 2- and 4-nitrocarbazole by the de-amination of/

of 2- and 4-nitro-3-aminocarbazole, prepared according to Kehrmann and Zweifel (44).



Kehrmann named the isomers, melting at 177°C and 233°C, α- and β-nitro-3-aminocarbazole, having obtained them by nitration of 3-diacetamidocarbazole with subsequent hydrolysis, but he was unable to distinguish them. Although the patent claims that de-amination of the α-derivative yielded 2-nitrocarbazole, the only evidence in support is the fact that reduction gave an amine melting at the same temperature (238°C) as that prepared by Blank (37) by pyrolysis of "diphenylin". Blank claimed to have isolated 2-aminocarbazole by this method, but gave no details concerning his starting material, presumably 2:4'-diaminodiphenyl, and no analysis figures were included for the final product/

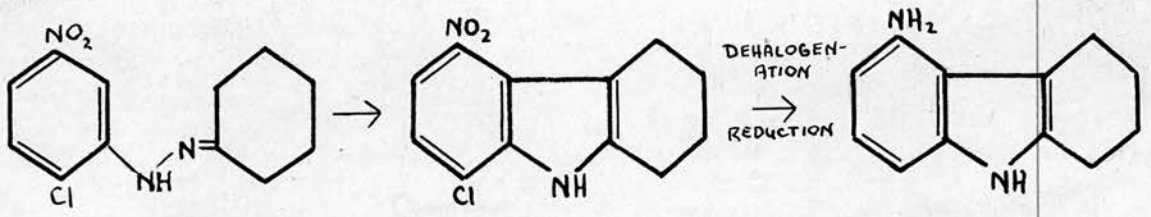
product:-



The so-called 4-nitrocarbazole was not described in the patent, but 2-nitrocarbazole was said to crystallise from benzene in orange-yellow needles, m.p. 175°C. No analysis was given. Authentic 2-nitrocarbazole is described in the literature as a pure yellow substance crystallising from benzene as plates and prisms, m.p. 165/6°C, and 4-nitrocarbazole as orange prisms, m.p. 179/80°C. They have been prepared by Barclay and Campbell (27) by dehydrogenation of 7- and 5-nitrotetrahydrocarbazole. A molecular compound of 5- and 7-nitrotetrahydrocarbazole, m.p. 154°C, prepared by applying the Borsche synthesis to cyclohexanone-m-nitrophenylhydrazone, was thought by Borsche and co-workers to be a single compound (23), but Plant (45) proved that it consisted of two isomers, and isolated the 7-isomer in a pure condition. Barclay and Campbell obtained pure samples of both isomers by chromatographic adsorption (27). Their constitution has been proved by reduction to the corresponding amines and comparison with 5-aminotetrahydrocarbazole obtained

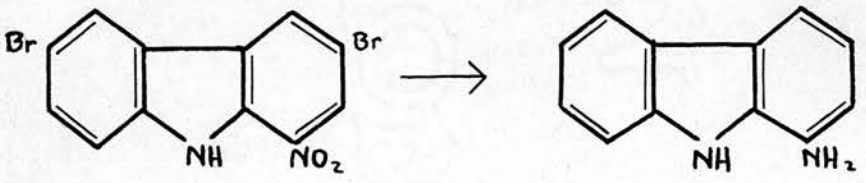
by/

by synthesis from cyclohexanone-2'-chloro-5'-nitrophenylhydrazone (45).



Of the other mono-nitro carbazoles, 3-nitrocarbazole is best prepared by direct nitration, usually of N-nitrosocarbazole with subsequent hydrolysis, and 1-nitrocarbazole by the method of Tucker and co-workers (p. 12) already described.

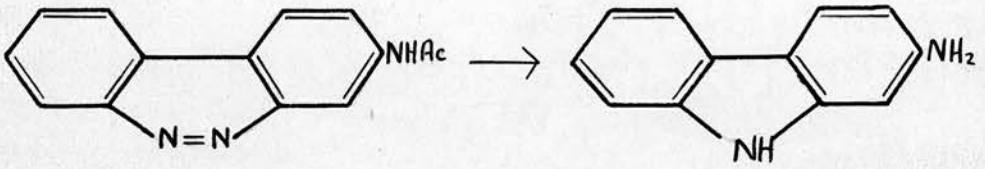
Reduction of 3- (44, 46) and 1-nitrocarbazole (47) yields the corresponding amines, but 1-aminocarbazole is prepared in good yield on treating 3:6-dibromo-1-nitrocarbazole with hydriodic acid, with resultant reduction of the nitro group and debromination (14).



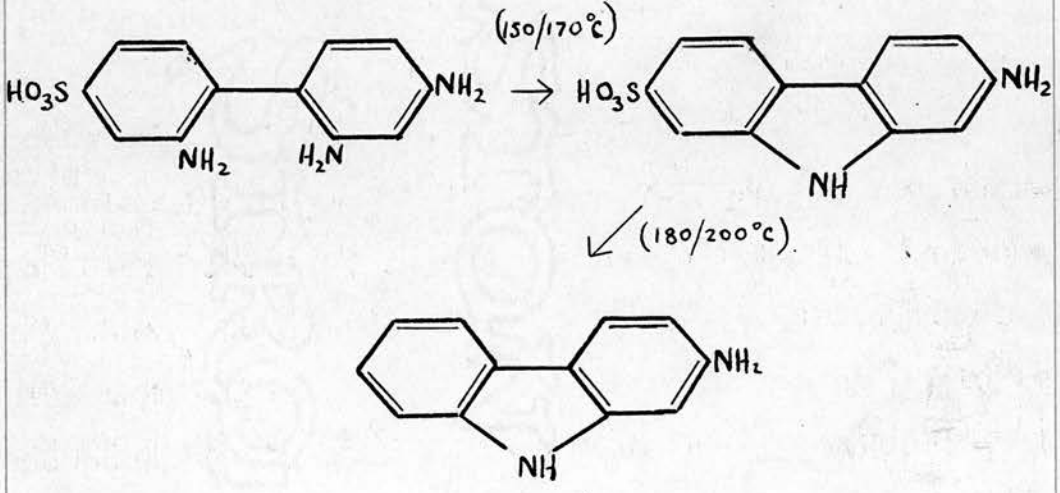
2-Aminocarbazole was possibly prepared by Blank in 1891 (37) by pyrolysis of diphenylin, and by King and Beer (48) by the hydrogenation of 3-acetamidobenzocinnoline with Raney nickel, and subsequent/

no analysis.
mp. 238°.
King
mp. 240° (d)
"believed to be"

subsequent hydrolysis.



In 1930 a German patent (49) claimed to have prepared 2-aminocarbazole (no melting-point or analysis was quoted) by heating 2:2':4'-triamino-diphenyl-4-sulphonic acid with dilute mineral acids at 150°/170°C, giving 2-aminocarbazole-7-sulphonic acid, and removing the sulphonic acid group by heating to 180/200°C.

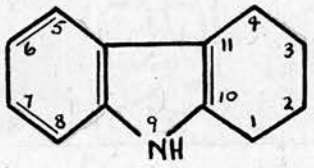


No description of 4-aminocarbazole can be found in the literature.

Tetrahydrocarbazole/

Tetrahydrocarbazole.

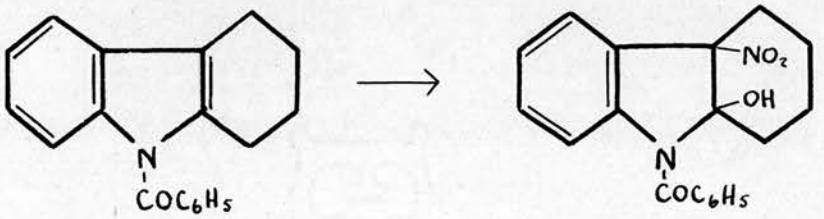
Tetrahydrocarbazole prepared by the Borsche synthesis from cyclohexanone phenylhydrazone is identical with the product obtained by reduction of carbazole with sodium and alcohol (50). Although it decomposes in the air if impure, recrystallisation from light petroleum gives a colourless, stable substance, m.p. 116°C.



Borsche, Witte and Bothe were unsuccessful in their attempts to obtain nitro derivatives of tetrahydrocarbazole by direct nitration (23), but Perkin and Plant (24) succeeded by treating a solution of tetrahydrocarbazole in sulphuric acid with potassium nitrite at -5°C, obtaining the 6-nitro-derivative. N-Methyltetrahydrocarbazole can be nitrated similarly in the 6-position, while N-acetyl- or benzoyltetrahydrocarbazole on nitration in glacial acetic acid solution gives 7-nitro-9-acetyl- or benzoyltetrahydrocarbazole.

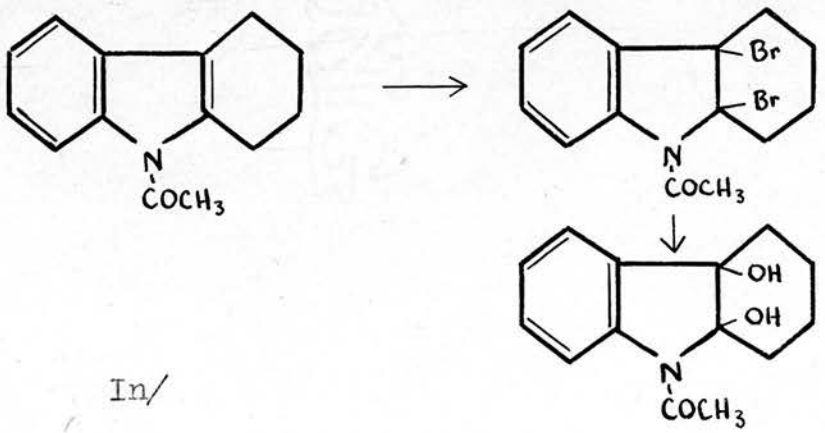
N-substituted tetrahydrocarbazoles can react in a different manner on nitration, however. N-Benzoyltetrahydrocarbazole, for example, yields, by/

by addition of nitric acid at the 10-11-double bond, 10-hydroxy-9-benzoyl-11-nitrohexahydrocarbazole (or possibly the 11-hydroxy-10-nitro-derivative).



N-Acetyltetrahydrocarbazole, on treatment with nitric acid, can give 10:11-dihydroxyhexahydrocarbazole.

The reactivity of the 10-11-double bond is again emphasised on bromination. The action of bromine on N-acylderivatives of tetrahydrocarbazole has been studied by Plant and Tomlinson(51) who showed that no appreciable substitution takes place. In each case a 10:11-dibromo derivative was obtained, but could only be isolated in the absence of water, which caused immediate hydrolysis to the corresponding dihydroxy compound in the case of N-acetyltetrahydrocarbazole.



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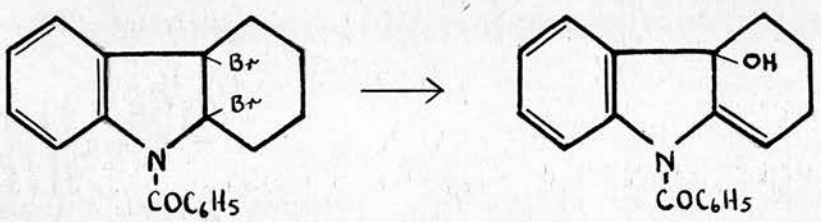
In the case of N-benzoyltetrahydrocarbazole, only one bromine atom is replaced by hydroxyl, the other being removed as hydro bromic acid to give 11-hydroxy-9-benzoyl-1:2:3:11-tetrahydrocarbazole.

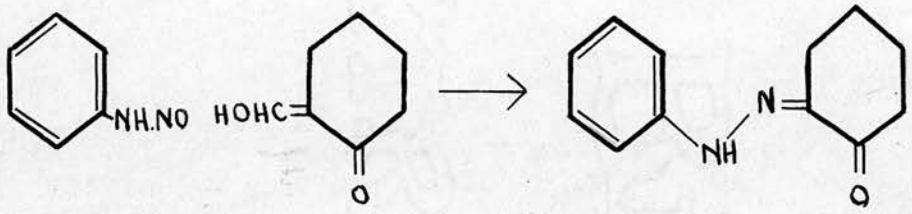


Bromination of tetrahydrocarbazole itself was found by Borsche and co-workers (23) to give a mixture of a tetrabromo and hexabromo derivative of uncertain structure, but Plant (52) showed that under certain conditions addition at the 10- and 11- positions again took place, isolating finally 10-hydroxy-1:2:3:10-tetrahydrocarbazole. This compound was also obtained on chlorination.

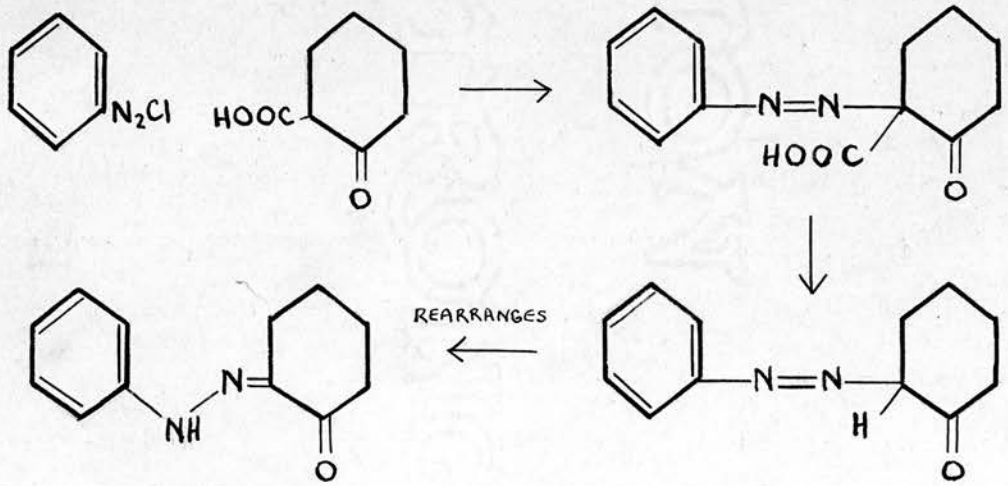
An interesting derivative of carbazole which has not yet been fully investigated is 1-ketotetrahydrocarbazole. This was first prepared by Coffey (53) in 1923 by treatment of the monophenylhydrazone of cyclohexane-1:2-dione with a mixture of glacial acetic and sulphuric acids, the preparation being a special case of Borsche's synthesis.

The presence of a keto-group in 1-ketotetrahydrocarbazole was shown by the preparation of a ketazine and a semicarbazide.

Cyclohexane-1:2-dionemonophenylhydrazone can be prepared by the action of oxymethylene cyclohexanone on diazotised aniline in neutral solution (53),

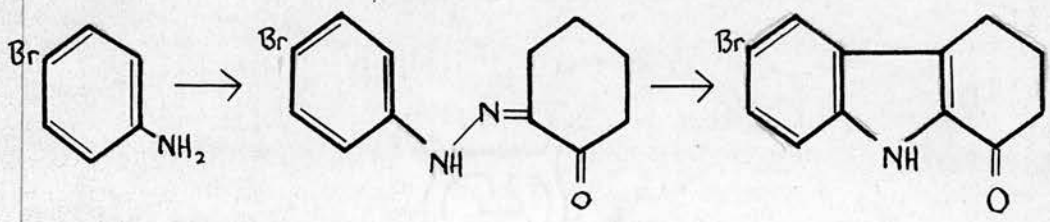


or by treating cyclohexanone-2-carboxylic acid with diazotised aniline and subsequent addition of sodium acetate.(54).

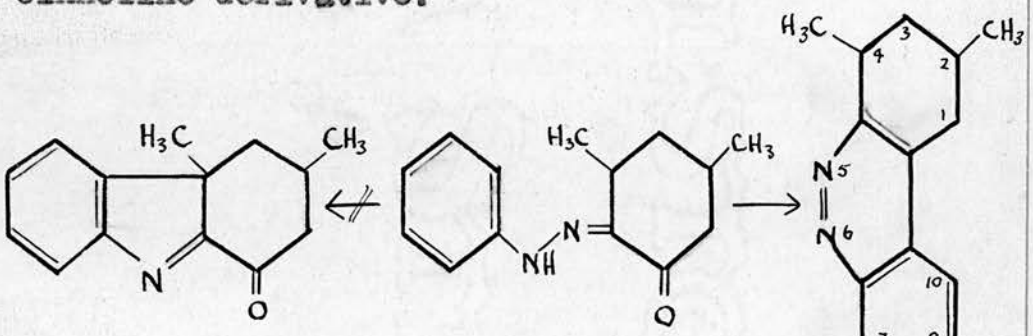


By the former method Mears, Oakeshott and /

and Plant (55) have prepared several derivatives of ketotetrahydrocarbazole from suitable substituted amines, e.g.,



While investigating the reaction, Moore (56) attempting to prepare 1-ketotetrahydrocarbazolenines, discovered that 4:6-dimethylcyclohexane-1:2-dione-1-phenylhydrazone when dissolved in concentrated sulphuric acid gave a good yield of a cinnoline derivative.



3:11-DIMETHYL-1-KETOTETRAHYDROCARBAZOLENINE

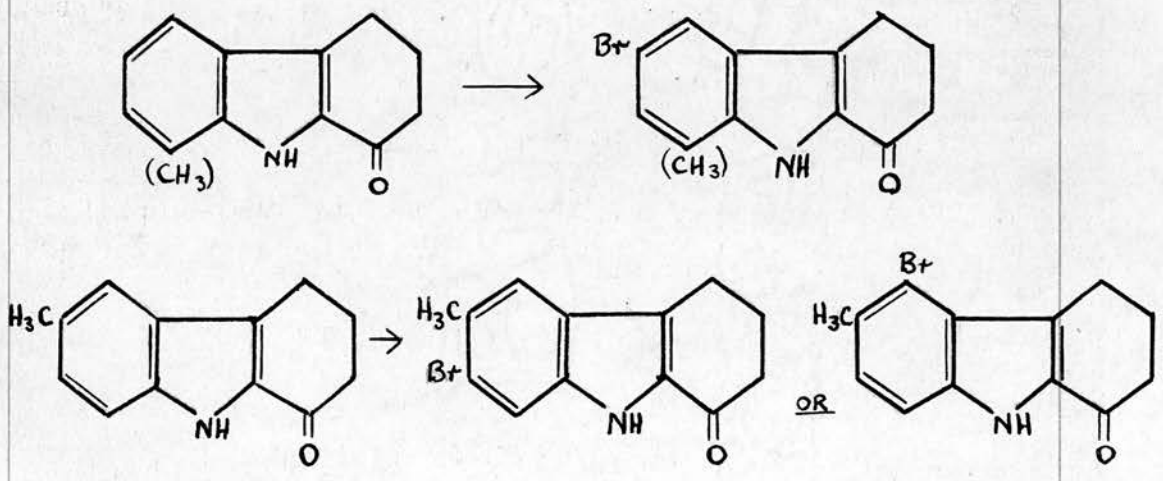
2:4-DIMETHYL-1:2:3:4-TETRAHYDROBENZOCINNOLINE

Similarly the unsubstituted cyclohexandione phenylhydrazone gave 1:2:3:4-tetrahydrobenzocinnoline.

The imino group in 1-ketotetrahydrocarbazole is much less reactive than in tetrahydrocarbazole; no acetyl derivative was isolated on boiling with acetic anhydride, even in the presence of a trace/

trace of sulphuric acid, and an attempt to benzoylate also failed. Ruberg and Small (57) have, however, prepared the N-methyl derivative by the method of Stevens and Tucker (42).

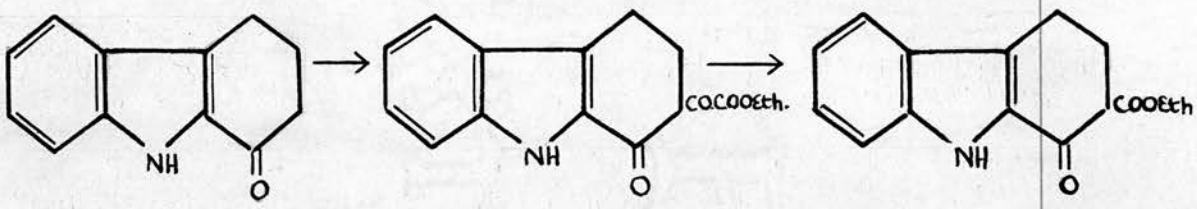
The reactivity of the 10-11-double-bond in tetrahydrocarbazole is greatly diminished in ketotetrahydrocarbazole. Reaction with an equimolar quantity of bromine was found to produce 6-bromo-1-ketotetrahydrocarbazole (55). 8-Methylketotetrahydrocarbazole also gave the 6-bromo-derivative, while 6-methylketotetrahydrocarbazole yielded either the 5- or 7-bromo-compounds.



The action of a mixture of nitric and sulphuric acids on ketotetrahydrocarbazole and its 6- and 8-methyl derivatives gave nitro-substitution in the same positions as above.

Elks/

Elks, Elliott and Hems (58) on treating ketotetrahydrocarbazole with ethyl oxalate in cold alcoholic sodium ethoxide obtained 1-ketotetrahydrocarbazole-2-glyoxalate which on heating lost carbon monoxide to form ethyl-1-ketotetrahydrocarbazole-2-carboxylate.



The direct introduction of a carbethoxy group into ketotetrahydrocarbazole with ethyl carbonate, or a formyl group with ethyl formate, was not achieved.

Reduction of ketotetrahydrocarbazole with red phosphorus and hydriodic acid gives tetrahydrocarbazole, while with tin and hydrochloric acid hexahydrocarbazole is formed.

Kent (59, 60) has shown that 1-ketotetrahydrocarbazole readily forms crystalline complexes with polynitro hydrocarbons, containing 1 molecule of the hydrocarbon and 2 or 1 molecules of the carbazole. The polynitro hydrocarbons included 1:3:5- and 1:2:4-trinitrobenzene, and m- and p-dinitrobenzene. This capacity is retained to some extent by the monomethyl homologues of ketotetra-

hydrocarbazole/

ketotetrahydrocarbazole, all of which were synthesised by Kent.

Although the monomethyl derivatives of ketotetrahydrocarbazole have been investigated, no dimethyl derivative appears to have been prepared. Such compounds, if suitably reduced, would yield dimethyltetrahydrocarbazoles which in many cases cannot be prepared successfully by the Borsche synthesis (see p. 9).

OBJECT OF RESEARCH.

An orientation of α-and β-nitro-3-aminocarbazole does not appear to have been carried out, but a nitrocarbazole prepared by de-amination of the former has been stated (43) to be 2-nitrocarbazole. Its description, however, does not agree entirely with that of authentic 2-nitrocarbazole, which has since been prepared by dehydrogenation of 7-nitrotetrahydrocarbazole (p. 14). An orientation of the α- and β-nitro-amines prepared by Kehrmann was therefore desirable, and was undertaken in this research. It was also decided to attempt the preparation of 2- and 4-aminocarbazole (the latter has not been described in the literature) and make a direct comparison of the former with the amine obtained by pyrolysis of 2:4'-diaminodiphenyl.

The Borsche synthesis of tetrahydrocarbazoles is often ineffective because of the instability of the intermediate substituted phenylhydrazines (e.g., dimethylphenylhydrazines). This difficulty can be overcome if the corresponding ketotetrahydrocarbazoles can be prepared and a suitable method of reduction applied. Extension of Coffey's synthesis may prove invaluable in such cases. Ketotetrahydrocarbazole might also be useful in the preparation/

preparation of 1-substituted alkyl carbazoles by reaction with Grignard reagents.

With these investigations in view this research was carried out, and to the results obtained and the problems arising therefrom this thesis is devoted.

EXPERIMENTAL SECTION - INTRODUCTION.

The experimental work carried out in the course of this research is described in the following pages. Yields obtained are quoted as percentages of the maximum theoretical amounts obtainable. Melting-points were determined on the apparatus described in "Qualitative Organic Chemistry" by Neil Campbell (p. 7, fig. 4) or on a micro melting-point apparatus (Kofler, Mikrochem 1934, 15, 242).

All new compounds obtained in the pure state were analysed by micro methods by Drs Weiler & Strauss of Oxford.

EXPERIMENTAL

Preparation of α-(2 or 4) Nitro-3-aminocarbazole and β-(4 or 2) Nitro-3-Aminocarbazole

The preparation was carried out by the method of Kehrmann and Zweifel (Helv. Chim. Acta, 1928, 11, 1213). Since minor but essential modifications were applied at certain stages, a full account of the method, with the exception of the preparation of 3- nitrocarbazole, is included.

Stage 1: Preparation of 3-Nitrocarbazole.

(Lindemann, B. 1924, 57, 555)

Carbazole (50g) on treatment with sodium nitrite and subsequent nitration, yielded N-nitroso-3-nitrocarbazole. Hydrolysis with caustic soda gave 3-nitrocarbazole, which was recrystallised from glacial acetic acid.

Yield = 34g. m.p. 205°C.

Stage 2: Preparation of 3-Aminocarbazole and its monoacetyl derivative

3-Nitrocarbazole (30g), finely powdered in a mortar, was suspended in alcohol (500 ml), and a solution of 90g stannous chloride (analytical reagent) in concentrated hydrochloric acid (500 ml) added in portions. The liquid was heated on the water/

water-bath until it became no clearer, and, after filtration, was distilled to one-third of its original volume. It was left standing at room temperature for 12 hours, and the double tin salt of the amine which had separated out as a dark heavy mass, was filtered, washed with concentrated hydrochloric acid and dried for some hours on the water-bath. The salt was ground thoroughly in a mortar with an equal weight of anhydrous sodium acetate, covered with five parts by weight of acetic anhydride and left for six hours with gentle stirring at room temperature. Excess anhydride was destroyed and sodium salts dissolved by the addition of cold water, and subsequent heating on the water-bath. The precipitate of tin hydroxide and the acetyl derivative of 3-aminocarbazole which remained were filtered, dried and extracted with hot alcohol. The extract was evaporated to the point of crystallisation and allowed to cool. The acetyl derivative now crystallised out but it was contaminated with a dark green material, and further recrystallisations were necessary to produce colourless needles. m.p. 215/216°C (lit. 217°C)

Yield of pure substance = 8g (25%).

A more satisfactory method of preparing 3-aminocarbazole, and thence its acetyl derivative, was that of Whitner (J.A.C.S. 1924, 46, 2326) who reduced/

reduced 3-nitrocarbazole with zinc and alcoholic caustic potash.

3-Nitrocarbazole (10g) and caustic potash (10g) were dissolved in alcohol (500 ml) and boiled under reflux with stirring. Zinc dust was added in portions at intervals of a few minutes until the deep red colour of the solution had disappeared. The rate of reduction depended on the efficiency of stirring, but generally took from one to two hours. The solution was filtered and poured into water and the amine, in the form of a grey solid, was filtered, dried and recrystallised from alcohol.

Yield = 5.5g m.p. 252/3°C (lit. 254°).

Acetylation of 3-Aminocarbazole.

3-Aminocarbazole (5g) was dissolved in glacial acetic acid and excess acetic anhydride added. On standing for several hours, crystals of the acetyl derivative separated, but only in small quantity. These were filtered, and the filtrate poured into water. A further quantity of 3-acetamidocarbazole was obtained. On recrystallising from alcohol, colourless prisms separated, m.p. 215°C.

Yield = 3.9g.

(% yield from $-NO_2 \rightarrow NHAc$ = 40%)

Stage 3/

Stage 3: The further acetylation of 3-acetamidocarbazole.

3-Acetamidocarbazole (10g) was treated with acetic anhydride (50 ml) and concentrated sulphuric acid (0.5 ml), and boiled for 45 minutes. The monoacetyl derivative dissolved to give a red solution, but soon a red solid appeared. The hot liquid was carefully poured into 500 ml. water and stirred thoroughly until a rusty red solid separated. After allowing to stand with occasional stirring for one hour longer, the liquid was filtered and the solid dried and extracted with benzene (Soxhlet extraction). On evaporation of the benzene a yellow crystalline solid was obtained, being a mixture of the di- and triacetyl derivatives of 3-aminocarbazole.

M.p. = 145/165°C.

yield = 11g.

Stage 4: Nitration of a mixture of Di- and Triacetyl-3-aminocarbazole.

A mixture of the acetyl derivatives (10g) was dissolved in about 60 ml. glacial acetic acid with warming, and the solution cooled to room temperature. To the cold solution was added dropwise a mixture of 5 ml. pure fuming nitric acid and 5 ml. glacial acetic acid, with stirring. Yellow crystals/

crystals began to appear after some time, but crystallisation was slow, α-nitro-3-diacetamidocarbazole coming down first in a pure condition, followed by a mixture of the α - and β-nitro compounds (see introduction, p. 13). The liquid was left overnight and the whole crystalline mass filtered off.

Yield = 6g
m.p. = 210/225°C

The attempted separation of α-and β-Nitro-3-diacetamidocarbazole by Chromatographic Adsorption.

When 3-diacetamidocarbazole is nitrated, after some time pure crystalline α-nitro-3-diacetamidocarbazole separates, followed by a mixture of the α- and β- compounds. This mixture, on hydrolysis, yields a mixture of the corresponding monoacetyl derivatives, one of which is much more readily soluble in alcohol than is the other. A separation of α- and β- nitro-3-acetamidocarbazole can thus be effected. An attempt was made, however, to separate the diacetyl compounds by chromatographic adsorption.

The above mixture (0.5g) was dissolved in the minimum of cold benzene and chromatographed (Alumina/

(Alumina, 18 x $\frac{3}{4}$ inch). The chromatogram was developed with benzene.

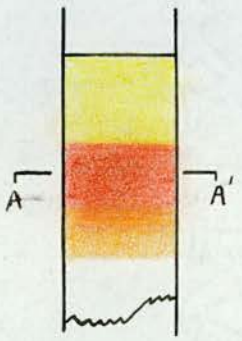


FIG. 1

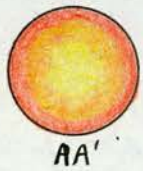


FIG. 2

A homogeneous yellow band at first appeared, moving very slowly. After 24 hours a red band began to appear, deepening in intensity, and merging into a third band, orange-red in colour (Fig. 1). Since the bands were moving very slowly, the chromatogram was dried, and each section extracted with alcohol.

The yellow band yielded only a few milligrams of the unchanged mixture of α- and β-nitrodiacetyl compounds.

When the red band was examined it was found that it was not homogeneous. Only on the circumference was it pure red (see Fig. 2) where the alumina was in contact with the glass. The colour became lighter gradually until in the centre it was yellow. The band on extraction yielded an orange solid. On recrystallisation from a little alcohol/

alcohol, a red solid remained undissolved. This was filtered and recrystallised from glacial acetic acid, giving scarlet needles, m.p. 275/7°C. The filtrate on evaporation gave the unchanged starting mixture.

The orange band had a similar appearance in cross section, without the deep red circumference, with a colour gradation towards the centre. It also yielded a red compound, m.p. 277°C, and unchanged starting mixture.

The red compound in each case was proved, by mixed melting-point with an authentic sample, to be α-nitro-3-acetamidocarbazole. The total yield of this was about 0.07g, while about 0.30g of the unchanged mixture of α-and β-nitro-3-diacetamidocarbazole was recovered.

Stage 5: α-Nitro-3-acetamidocarbazole and its conversion to α-Nitro-3-aminocarbazole.

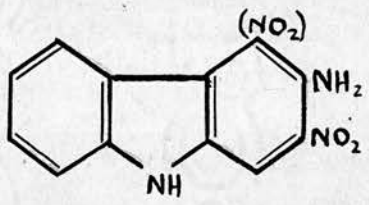
The mixture of α-and β-nitro-3-diacetamidocarbazole (4g) was ground in a mortar with concentrated alcoholic caustic soda until on adding a drop of the red liquid to water, no trace of a yellow solid could be seen. The liquid was filtered, leaving a bright red residue which was recrystallised from alcohol to give red needles, m.p. 275°C, of α-nitro-3-acetamidocarbazole (Lit. 274°C).

The filtrate contained the β-nitro isomer.

The/

The α-nitroacetamido derivative was heated on the water-bath with alcoholic hydrochloric acid (1:1 by volume) until no more red particles could be seen. The hydrochloride of α-nitro-3-aminocarbazole began to separate out as brown needles. The liquid was cooled, diluted with water and saturated with gaseous ammonia, whereupon a violet solid, the free amine, separated out. Recrystallised from alcohol, violet needles were obtained.

Yield = 1.8g
m.p. = 233°C. (Lit.)



α - NITRO - 3 - AMINOCARBAZOLE

Stage 6: β-Nitro-3-acetamidocarbazole and its conversion to β-Nitro-3-aminocarbazole.

Many attempts to isolate β-nitro-3-acetamidocarbazole were unsuccessful. In each case the filtrate assumed to contain this product (p. 34) was poured into water, yielding a red solid which was filtered and dried. On attempted recrystallisation from alcohol and benzene the solid separated in an amorphous condition, with a wide/

wide melting range.

In one instance the melting point was about 180/210°C. An attempt to obtain β-nitro-3-acetamidocarbazole from the mixture by chromatographic adsorption did not succeed. The solid (about 0.5g) was dissolved in benzene and chromatographed (alumina, 10 x ½ inch), the chromatogram being developed with benzene. After several hours a slight separation was noticed into a dark red-brown band above, and a violet band below (see Fig. 3). Thirteen portions of eluate were evaporated and the residues examined. The first three yielded a total of 0.05g α-nitro-3-aminocarbazole m.p. 233°C, on recrystallisation. The other portions all gave mixtures whose melting range was at least 10°, lying between 180° and 210°, which could not be further purified by recrystallisation. These were thought to be mixtures of β-nitro-3-acetamidocarbazole , α-nitro-3-aminocarbazole, and, possibly, β-nitro-3-aminocarbazole. Thus it seems that treatment with alcoholic caustic soda will cause complete hydrolysis if continued beyond a certain time.

FIG. 3

FIG. 4

On another occasion hydrolysis was incomplete, but β-nitro-3-acetamidocarbazole was isolated by chromatographic adsorption. The crude solid (about 0.6g) obtained from the mother-liquor after hydrolysis with caustic soda was dissolved in benzene and chromatographed as above. The chromatogram was developed with benzene, the liquid being allowed to flow through the column at twice the normal rate, and a good separation was obtained in the course of one day into violet-brown and yellow bands (Fig. 4). The eluate from the latter was evaporated leaving a yellow solid, m.p. 189/195°C, probably a mixture of the unchanged diacetyl isomers (c.f. p. 32). The chromatogram was dried, the brown band cut and extracted with alcohol, and the extract evaporated, giving a brown solid. Recrystallisation from alcohol yielded rusty-red needles, m.p. 197/8°C. (Lit. 198°C.)

Analysis: $C_{14}H_{11}O_3N_3$	Requires	Found
% Carbon	62.40	62.49
% Hydrogen	4.12	4.51

The yield was so small, however, that further hydrolysis was not attempted.

The most successful attempt to obtain β-nitro-3-acetamidocarbazole resulted also in the isolation of β-nitro-3-diacetamidocarbazole, which/

which was not separated by Kehrmann, and was carried out as follows:- A mixture of α-and β-nitro-3-diacetamidocarbazole (5g) was ground in a mortar with concentrated alcoholic caustic soda for 15 minutes, and filtered to remove α-nitro-3-acetamidocarbazole. The filtrate was poured into water, precipitating a red solid which was filtered, dried and dissolved in the minimum of boiling alcohol. On cooling, an orange-red solid (R) separated, and was removed by filtration. The filtrate was reduced in volume, whereupon brown needles of β-nitro-3-acetamidocarbazole separated. Recrystallisation from alcohol yielded rust needles m.p. 198°C

Yield = 1.5g.

The orange-red solid (R) on recrystallisation from alcohol gave lustrous yellow elongated prisms, m.p. 224°C. A mixed melting-point with α-nitro-3-diacetamidocarbazole (m.p. 226°C) showed a depression of nearly 30°. The solid was assumed to be β-nitro-3-diacetamidocarbazole.

Analysis: $C_{16}H_{13}O_4N_3$	Requires	Found
% Carbon	61.73	61.72
% Hydrogen	4.18	3.89

The/

The final hydrolysis of β-nitro-3-acetamidocarbazole was carried out in a fashion similar to that of the α-isomer. After neutralisation with ammonia, however, the free amine was extracted with ether, and the ether layer separated, dried and evaporated. The amine in the form of a dark red-brown solid was recrystallised with difficulty from alcohol to give deep red needles, m.p. 175/177°C (Lit. 177°C).

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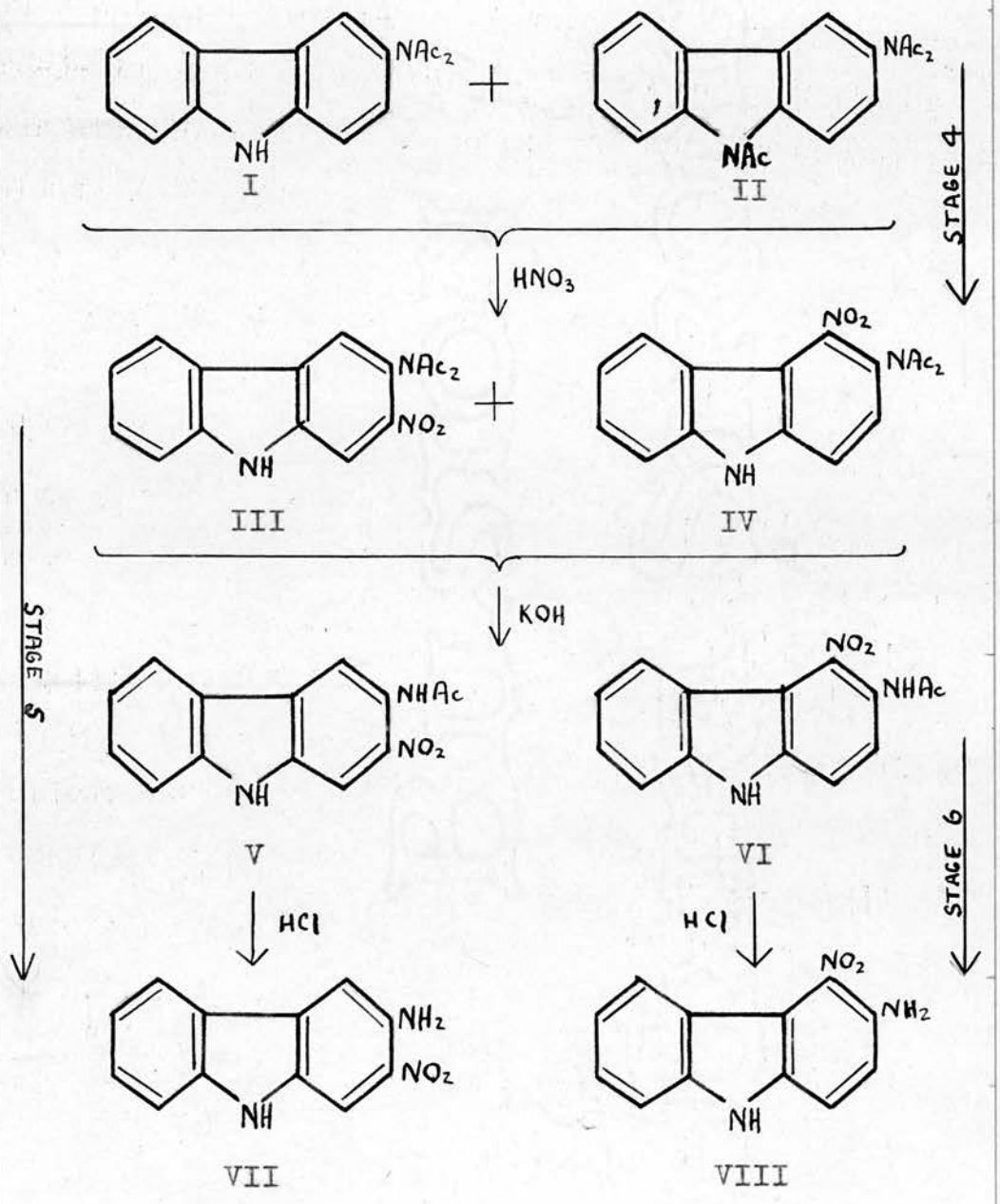
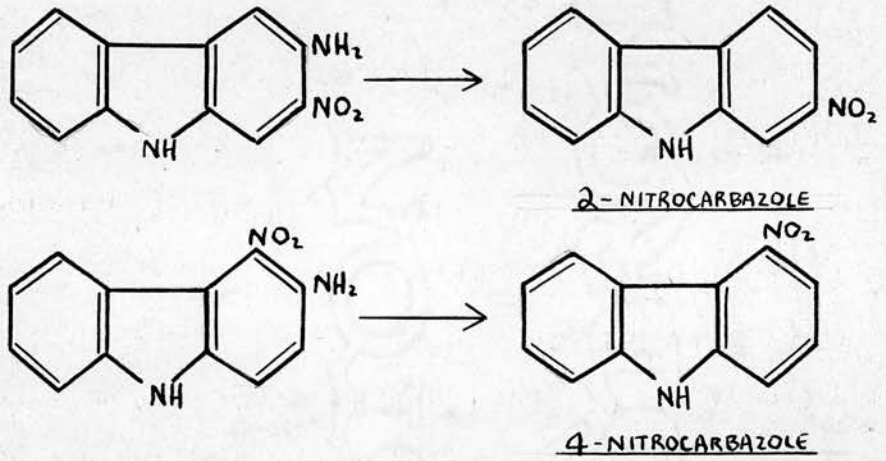
SUMMARY OF STAGES 4 to 6.



I, II	A mixture of Di- and Triacetyl-3-aminocarbazole
III	2-Nitro-3-diacetamidocarbazole
IV	4-Nitro-3-diacetamidocarbazole
V	2-Nitro-3-acetamidocarbazole
VI	4-Nitro-3-acetamidocarbazole
VII	2 (α or β)-nitro-3-aminocarbazole
VIII	4 (α or β)-nitro-3-aminocarbazole.

The preparation of 2- and 4-Nitrocarbazole by the method described in B.P. 340,550.



α-Nitro-3-aminocarbazole (0.2g) prepared by Kehrmann's method was dissolved in boiling alcohol and 0.3g 20% alcoholic sulphuric acid added. The liquid was cooled to 0° and diazotised with a solution of sodium nitrite (0.08g) in 0.14 ml. water. The clear diazo solution was boiled on the water-bath for about 30 minutes, and distilled to small volume. Water was added to the hot solution until it was turbid and when cool a dark brown solid separated. Recrystallisation from benzene (charcoal) gave lustrous yellow needles, m.p. 171/173°. A further recrystallisation raised the m.p. to 173°C. A mixed melting-pdint with 4-nitrocarbazole prepared by Barclay and Campbell (J. 1945, 530) showed a depression of about 20°. Admixture with 2-nitrocarbazole (m.p. 165/6°) gave a melting-point of 166/7 /

166/7°, showing that the derivative is also 2-nitrocarbazole.

The experiment was repeated with β-nitro-3-aminocarbazole (0.1g). When the volume of solution was reduced after diazotisation and boiling, and water added, a dark sticky solid separated. It was extracted with ether and the extract dried over anhydrous sodium sulphate and evaporated, leaving a brown oily solid. This was dissolved in a few ml. benzene and chromatographed (alumina 3 x ½ inch). A yellow band separated in the column, and the eluate from this band evaporated leaving an orange-yellow solid which was further purified by sublimation.

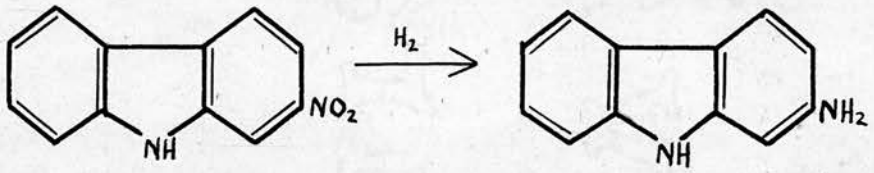
Since only a few milligrams of solid were obtained from the chromatogram, a micro-sublimation was carried out. The solid sublimed in the form of yellow-orange plates, m.p. 179/80°C. Authentic 4-nitrocarbazole under similar conditions gave plates of the same appearance, m.p. 179/80°C. A mixture of the two sublimates also melted at 179/80°C.

The compound obtained by removing the amino-group from β-nitro-3-aminocarbazole is thus 4-nitrocarbazole.

This preparation of 4-nitrocarbazole was repeated on a 1g scale. Extraction with ether was followed on this occasion by extraction with 5 ml. boiling/

boiling xylene, after which the extract wascooled and chromatographed (alumina 3 x 1 inch). A yellow band appeared as before, but four portions of eluate from this yielded only an oil which solidified on trituration with alcohol, giving a colourless amorphous solid almost insoluble in alcohol, very soluble in benzene. This solid was not investigated further.

The reduction of 2-Nitrocarbazole to 2-Aminocarbazole with platinum as catalyst.



Platinic oxide was prepared as described in "Organic Syntheses" 8, 92, and the apparatus used for the reduction was similar to that described in the same volume, p. 10.

It was desired to calibrate the reduction apparatus by reducing 1/100 mol benzil, dissolved in 100 ml alcohol, with 0.02g catalyst. A very small pressure drop was observed over a period of 20 minutes, however, and when a blank was carried out the same pressure drop occurred. The experiment was repeated with benzoin in alcohol, but this also was unsatisfactory. Benzene and glacial/

glacial acetic acid were used as solvents without success.

The next experiment wasattempted with 2.1g benzoin (1/100 mol), 100 ml. alcohol and 0.1g of the catalyst. A blank was carried out giving a drop in pressure of 2.5 lb/sq. in. in 10 minutes. The benzoin was added and a further pressure drop of 10 lb/sq. in. obtained in 40 minutes. The liquid was filtered and reduced in volume, hydrobenzoin crystallising out in colourless plates, M.p. 130/5°C. Recrystallisation from alcohol raised the melting-point to 138°C. A mixture of this substance with benzoin melted at about 110°C.

α-Nitronaphthalene was reduced to α-naphthylamine successfully. The nitro-compound (1/300 mol) gave a pressure drop of 9.5 lb/sq. in. in 24 minutes. An oil was obtained which solidified on stirring. The acetyl derivative was prepared and recrystallised from aqueous alcohol. M.p. 157/9°C.

3-Nitrocarbazole (m.p. 205°C) was reduced to 3-aminocarbazole, m.p. 249/51°C, which was obtained By evaporation of the solvent and recrystallisation from aqueous alcohol.

2-Nitrocarbazole (0.2g) dissolved in 100 ml. alcohol, was reduced in the presence of 0.1g catalyst. A 3 lb/sq. in. drop (as calculated) was obtained in 4 minutes, and no further drop had occurred/

occurred after 15 minutes. The liquid was filtered, reduced in volume, hot water was added and it was allowed to cool. Pale violet needles, m.p. 233/6°C, separated out. Darkening occurred over the range 205/220°C. The solid crystallised from aqueous alcohol in colourless needles, rapidly darkening, m.p. 238/9°C. Rapid darkening also took place in solution.

Yield of pure compound = 0.04g (25%)

The amine, treated with concentrated sulphuric acid and one drop of concentrated nitric acid, gave a deep blue-green colour, while with sulphuric and selenic acids, an emerald green colour was obtained.

Analysis: $C_{12}H_{10}N_2$	Requires	Found
% Carbon	79.1	78.3
% Hydrogen	5.5	5.7
% Nitrogen	15.4	14.9

The attempted reduction of 4-Nitrocarbazole to 4-Aminocarbazole

4-Nitrocarbazole (0.25g) prepared as described on p. 51 , was dissolved in alcohol, and reduction attempted as above. A pressure drop of 5 lb/sq. in. was obtained in 10 minutes, no further drop being noted after another 12 minutes. The colourless solution was filtered and reduced to small/

small volume, by which time it had become very dark in colour. After standing overnight water was added, precipitating a brown solid, which was filtered and dried. Attempts to recrystallise the solid from aqueous alcohol, benzene and light petroleum met with no success. The melting point of the crude solid was 170/5°C.

The remainder of the solid was dissolved in alcohol and a mixture of acetyl chloride (1 ml) and pyridine (2 ml) added. No crystallisation occurred overnight. The mixture was diluted with water, precipitating a grey solid which was filtered, dried and extracted with benzene (a few ml). The extract was purified by chromatography (alumina 6 x ½ inch). A dark impurity was adsorbed at the top of the column, and a pale violet band moved slowly downwards. Several portions of eluate yielded no solid, so the column was dried, cut and the portion containing the violet band extracted with alcohol. Evaporation gave a syrup. By crystallisation from aqueous alcohol colourless crystals were obtained in very small yield. M.p. 169/174°C.

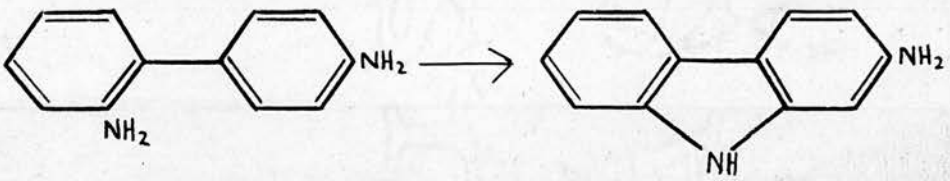
Recrystallisation from a mixture of benzene and light petroleum yielded colourless needles, m.p. 183/5°C.

Analysis/

Analysis: $C_{14}H_{12}ON_2$	Requires	Found
% Carbon	75.0	75.3
% Hydrogen	5.4	6.0
% Nitrogen	12.5	12.3

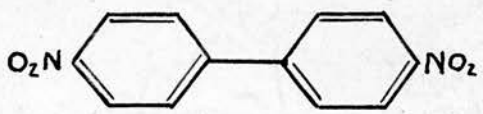
The compound was assumed to be 4-acetamidocarbazole. Since more 4-nitrocarbazole was not readily available, the experiment was not repeated.

The preparation of 2 (?) - Aminocarbazole by the method of Blank (B, 1891, 24, 306)

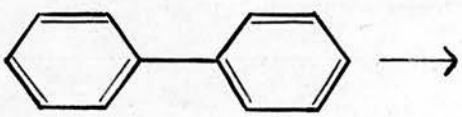


2:4'- DIAMINODIPHENYL — 2- AMINOCARBAZOLE

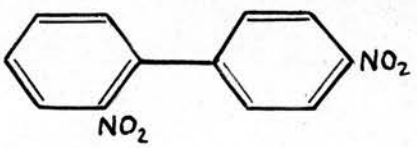
Stage 1: Preparation of 2:4'-Dinitrodiphenyl.



4:4'- DINITRODIPHENYL



DIPHENYL



2:4'- DINITRODIPHENYL

Diphenyl/

Diphenyl (20g) was dissolved in glacial acetic acid (35 ml) and to the solution fuming nitric acid was added slowly, the mixture being cooled occasionally in water. The solution was heated gradually to the boiling point and allowed to stand overnight. Pale yellow needles of 4:4'-dinitrodiphenyl crystallised and were filtered and dried. They were not recrystallised.

M.p. 236/8°C (Lit. 237°)

Yield 10g.

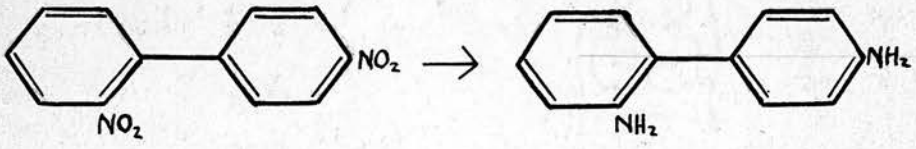
The filtrate was treated with water, and the solid which separated was recrystallised from alcohol to give pale yellow prisms of 2:4'-dinitrodiphenyl.

M.p. 94/5°C (Lit. 93/4°C)

Yield 8g.

Total yield = 18g (57%)

<u>Stage 2: The reduction of 2:4'-Dinitrodiphenyl to 2:4'-Diaminodiphenyl</u>.

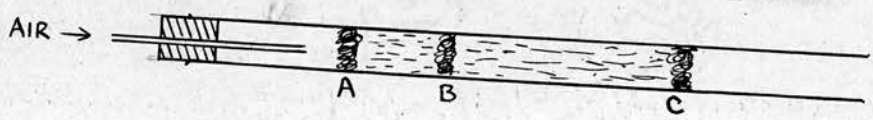


The quickest and most convenient way of carrying out this reduction was found to be with hydrogen with platinum as catalyst. Platinic oxide was prepared as described in "Organic Syntheses" 8, 92, and the reduction carried out in the/

the apparatus described in the same volume (p. 10).

2:4'-Dinitrodiphenyl (5g) was dissolved in 300 ml alcohol, platinic oxide (0.1g) was added, and on reduction a drop in pressure of hydrogen of 153 lb/sq. in. was recorded. The calculated drop from a standardising experiment was 150 lb/sq. in. The solution was filtered to remove the catalyst, and reduced in volume. Since no solid crystallised out, the alcohol was evaporated off leaving an oil which could not readily be obtained in solid form either by attempted crystallisation from or trituration with the usual solvents. (Lit. m.p. 50°C).

Stage 3: Pyrolysis of an oil assumed to consist mainly of 2:4'-Diaminodiphenyl.



A combustion tube, 36 inches in length, was fitted at one end with a holed stopper through which passed a glass tube so that a gentle stream of air could be passed through. A section of the tube BC, 18 inches long, was packed loosely with lime, enclosed with glass wool at B and C. The tube was strongly heated in a furnace, held in a sloping position as shown, and a stream of air passed/

passed through, to drive out any moisture which was present. The tube was allowed to cool and the oil which had been obtained by reduction of 2:4'-dinitrodiphenyl was absorbed in lime and placed in section AB. It was enclosed by glass wool placed at A. Section BC was now heated to redness, followed by AB. Soon a brown liquid appeared at the cool open end of the combustion tube and solidified rapidly. A portion was extracted with alcohol and the extract filtered and reduced in volume. The solid which separated, m.p. 227/30°C, was recrystallised from a mixture of benzene and light petroleum giving colourless needles, m.p. 238°C, which soon darkened to a brown colour. The yield was small.

With concentrated sulphuric acid + one drop concentrated nitric acid, a deep bottle green colour, characteristic of many carbazoles, was obtained.

A mixed melting-point of this substance and authentic 2 -aminocarbazole, obtained by reduction of 2-nitrocarbazole, showed no depression.

Analysis: $C_{12}H_{10}N_2$	Requires	Found
% Carbon	79.09	79.07
% Hydrogen	5.53	5.65
% Nitrogen	15.39	15.30

Preparation/

Preparation of 2- and 4-Nitrocarbazole by the dehydrogenation of 7- and 5-Nitro 1:2:3:4 - Tetrahydrocarbazole (Barclay and Campbell, J. 1945, 53o).

m-Nitrophenylhydrazine hydrochloride (12.3g), prepared by the method of Bischler and Brodsky (B. 1889, 22, 2809), was suspended in alcohol (60 ml) and boiled with 6 ml cyclohexanone for 40 minutes. The liquid was filtered, diluted with water and well shaken, and the orange nitrophenylhydrazone which separated was filtered, washed and boiled with a mixture of 10 ml concentrated sulphuric acid and 90 ml water for 45 minutes. A red solid was obtained and recrystallised from benzene, m.p. 151/2°C. (Lit. 154/5°C).

Yield = 11.6g.

This molecular compound of 5- and 7-nitrotetrahydrocarbazole was dissolved in 800 ml benzene and chromatographed (alumina, 24 x 2 inch). The column was developed with a mixture of benzene and light petroleum (3:1). A very good separation was obtained, approximately 4g of each isomer being obtained pure, while a small quantity only of the unchanged molecular compound was also isolated.

5-Nitrotetrahydrocarbazole (2g) was dehydrogenated with chloranil in xylene solution. a/

An/

An orange solid was obtained and recrystallised from benzene to give deep orange prisms, m.p. 179°C (Lit. 179/80°C).

Yield of pure product = 0.55g

In a similar manner 2-nitrocarbazole was obtained from 7-nitrotetrahydrocarbazole in corresponding yield, crystallising from benzene in yellow prisms, m.p. 172°C.

Preparation of the Monophenylhydrazone of Cyclohexane-1:2-dione, and its cyclisation to form 1-Keto-1:2:3:4-tetrahydrocarbazole.
(Coffey, Rec. trav. chim. 1923, 42, 529)

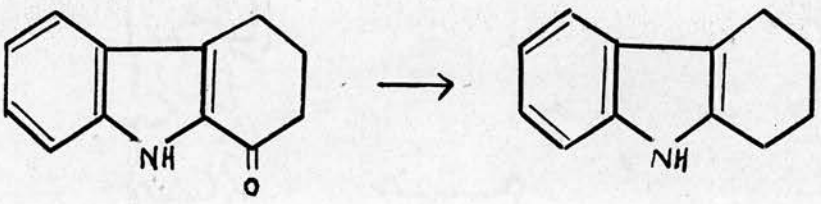
The synthesis of 1-ketotetrahydrocarbazole required the sodium derivative of oxymethylene cyclohexanone, condensation of the latter with benzene diazonium chloride, and ring-closure of the resulting phenylhydrazone with elimination of ammonia.

Yield of cyclohexone-1:2-dione monophenylhydrazone = 33%; m.p. 183/5°C (lit.)

Yield of 1-ketotetrahydrocarbazole = 55%; m.p. 170°C (lit. 169/70°C).

The brown impurity which contaminated 1-ketotetrahydrocarbazole was best removed by running a solution of the substance in benzene through a short column (alumina 6 x ½ inch). After this treatment and evaporation of the solvent, the product was obtained in a colourless condition.

The reduction of 1-Ketotetrahydrocarbazole by the method of Clemmensen.



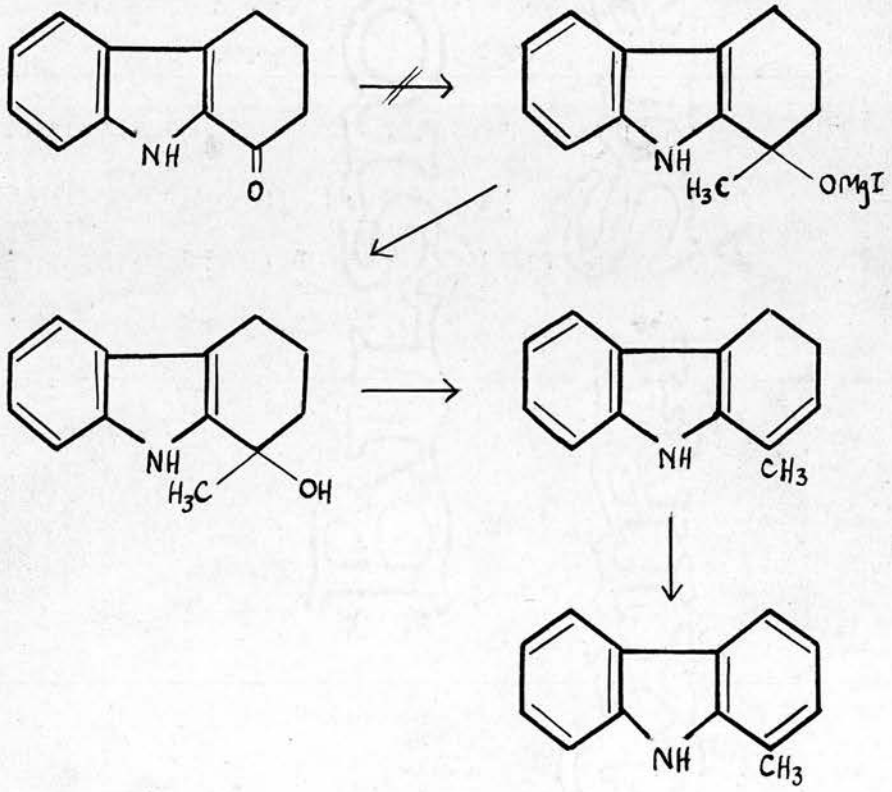
Zinc dust (30g) and mercuric chloride (3.0g) were shaken vigorously with water (40 ml) and concentrated hydrochloric acid (1.5 ml) for five minutes. The liquid was decanted and the resulting amalgamated zinc washed several times with water by decantation.

1-Keto-1:2:3:4-tetrahydrocarbazole (1g) dissolved in the minimum of alcohol was added in portions at intervals over a period of three hours to a boiling mixture of amalgamated zinc (25g), water (3 ml) and concentrated hydrochloric acid (7 ml). Concentrated hydrochloric acid (10 ml) was gradually added over the same period. The mixture was boiled for a further 3 hours, the solution decanted, the amalgam washed twice with 5 ml portions of hot alcohol and the washings added to the decanted solution. The solution was evaporated slightly, water was added, and the resulting white cloudy precipitate extracted twice with ether. The extract was dried/

dried over anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from light petroleum (100/120°C) giving white plates, m.p. 113/14°C. (Lit. 116°C).

Mixed melting-point with authentic tetrahydrocarbazole was 112/114°C. Yield of pure product was 0.5g (55%).

The attempted preparation of 1-Methylcarbazole.



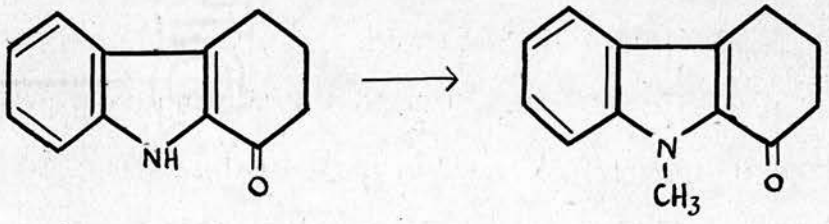
A small crystal of iodine was added to Grignard magnesium (0.12g) and a few drops of a solution of methyl iodide (0.5 ml) in anhydrous ether (15 ml) added. When reaction commenced (slight heating required), the rest of the solution of methyl iodide was gradually added. The mixture was stirred under reflux, until all the magnesium had disappeared, the solution was cooled and a solution of 1-ketotetrahydrocarbazole (0.93g) in anhydrous ether (100 ml) slowly added with vigorous stirring. After boiling for one hour, the liquid was poured into a mixture of dilute hydrochloric acid (30 ml) and ice (50g), and thoroughly stirred. The ether layer was separated, washed successively with water, aqueous solutions of sodium bicarbonate, sodium bisulphite and sodium bicarbonate, and water, dried over anhydrous sodium sulphate, and evaporated. A pale yellow solid was obtained which on recrystallisation from alcohol gave almost colourless needles, m.p. 169°C. Mixed melting point with authentic 1-ketotetrahydrocarbazole was 167/8°C.

The above experiment was repeated. In this case a solution of 1-ketotetrahydrocarbazole in 100 ml ether was added to a solution made by adding 1.0 ml methyl iodide in 30 ml ether to 0.24g Grignard magnesium. After the ketone had all been added, the mixture was boiled and stirred for 24 hours/

hours before pouring into ice and hydrochloric acid. After separation of the ether layer, washing as before and drying over anhydrous sodium sulphate, a yellow solid was obtained, m.p. 167/9°C. A mixed melting point with 1-ketotetrahydrocarbazole showed no depression.

The experiment was carried out in a similar fashion with anhydrous anisole instead of ether. The compound which was isolated at the end of the reaction, on recrystallisation from alcohol, gave pale yellow needles, m.p. 170°C. Mixed melting-point with authentic 1-ketotetrahydrocarbazole 170°C.

Preparation of N-Methyl-1-keto-1:2:3:4-tetrahydrocarbazole (Ruberg and Small, J.A.C.S., 1938, 60, 1591)



The N-Methyl derivative of 1-ketotetrahydrocarbazole was prepared by the method of Stevens and Tucker (J.C.S. 1923, 2140)

1-ketotetrahydrocarbazole (3.6g)

Dimethyl sulphate (3.2 ml)

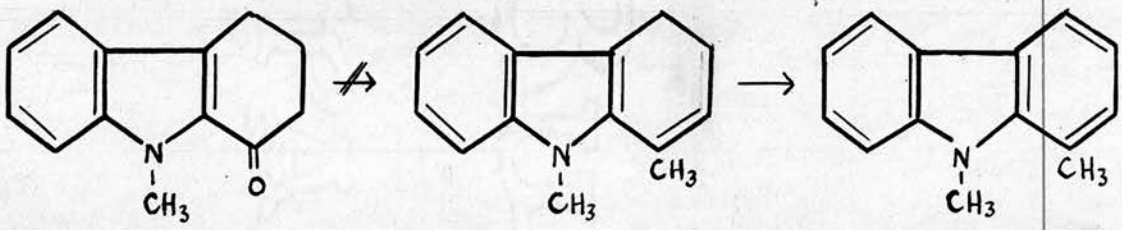
Acetone (16 ml)

Sodium hydroxide (3.2g) in water (2 ml)

Yield/

Yield = 3g (77%) m.p. 101°C/103°C
(Lit. 101.5/103.5)

The attempted preparation of 1:9-Dimethylcarbazole.

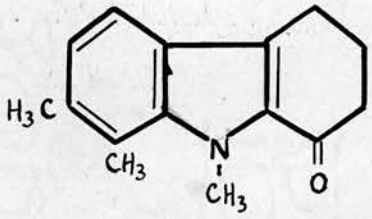


The experiment was carried out as described previously in the case of 1-ketotetrahydrocarbazole. N-Methyl-1-ketotetrahydrocarbazole (0.75g) dissolved in anhydrous ether was added gradually with stirring to a solution obtained by adding a mixture of 0.8 ml methyl iodide and 20 ml anhydrous ether to 0.18g Grignard magnesium (double the theoretical quantities). The mixture was boiled under reflux for 24 hours, and yielded a product which was shown by melting-point and mixed melting-point to be unchanged N-methyl-1-ketotetrahydrocarbazole.

Another experiment was attempted with anhydrous anisole instead of ether, but again the starting material was recovered unchanged.

Preparation/

Preparation of 7:8:9-Trimethyl-1-keto-1:2:3:4-tetrahydrocarbazole

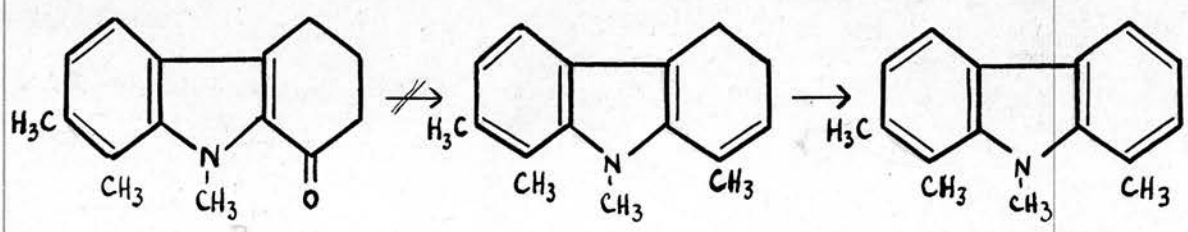


The compound was prepared by the method of Stevens and Tucker (J.C.S. 1923, 2140).

7:8-Dimethyl(keto)tetrahydrocarbazole (1.1g), (p. 64) methyl sulphate (0.8 ml) and acetone (4 ml) were mixed with a solution of sodium hydroxide (0.8g) in 0.5 ml. water, shaken vigorously and poured into water. A white solid was precipitated. On filtration and recrystallisation from methyl alcohol colourless prisms were obtained, m.p. 157/8°C.

Analysis: $C_{15}H_{17}ON$	Required	Found
% Carbon	79.30	78.83
% Hydrogen	7.49	7.73
% Nitrogen	6.17	5.91

The attempted preparation of 1:7:8:9-Tetramethyl-carbazole.



The/

The experiment was carried out as described in the case of 1-ketotetrahydrocarbazole. The Grignard reagent was made by the addition of a mixture of methyl iodide (0.5 ml) and anhydrous ether (15 ml) to 0.15g Grignard magnesium. To the stirred solution was added slowly a dry ethereal solution of 1-keto-7:8:9-trimethyltetrahydrocarbazole; the mixture was heated under reflux on the water-bath for several hours. After acidifying by pouring into hydrochloric acid and ice, washing and drying over anhydrous sodium sulphate, the ethereal solution was evaporated to dryness, leaving a yellow solid, m.p. 153/8°C. Recrystallised from methyl alcohol, it gave almost colourless prisms, m.p. 157/8°C, a mixed melting-point with 1-keto-7:8:9-trimethyltetrahydrocarbazole (m.p. 157/8°C) showing no depression.

Preparation of the Mono-o-tolylhydrazone of Cyclohexane-1:2-dione, (Mears, Oakeshott and Plant, J. 1934, 272).

This hydrazone was prepared by Coffey's method (Rec. trav. chim. 1923, 42, 529). O-Toluidine (19g) was dissolved in a mixture of 75 ml concentrated hydrochloric acid and 150 ml water, cooled to 0°C and diazotised with a solution of sodium nitrite (15g) in 60 ml water. After neutralisation with dilute caustic/

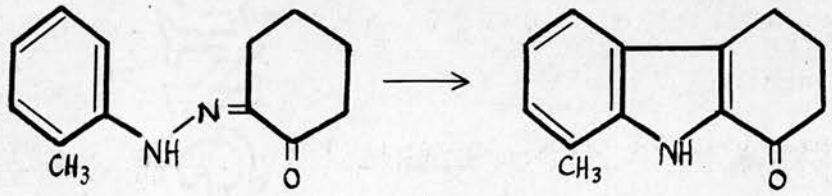
caustic soda at 0°C and the slow addition of oxymethylene cyclohexanone, a yellow solid slowly separated. Stirring was continued for some time until coagulation had taken place. The solid, now a light brown colour, was filtered, dried and recrystallised from alcohol. m.p. 95/6°C.

Yield of pure product was 10g (26%).

A sample was recrystallised from light petroleum (100/120°C) giving deep red prisms. m.p. 95/96°C. (Lit. 95/96°C).

Analysis: $C_{13}H_{16}ON_2$	Requires	Found
% Carbon	72.21	72.18
% Hydrogen	7.41	7.50

1-Keto-8-methyltetrahydrocarbazole.



When the above phenylhydrazone (5g) was boiled gently for 30 minutes with a mixture of 20 ml glacial acetic acid and 8 ml concentrated hydrochloric acid, and poured into water (50 ml), a brown solid immediately separated. After allowing the liquid to cool, this was filtered, dried, dissolved in the minimum of cold benzene, and purified/

purified by chromatographing (alumina 6 x 1 inch). A small dark band of impurity remained at the top of the column, whilst the eluate, almost colourless, yielded on evaporation a very pale pink solid. Recrystallisation from light petroleum (100/120°) gave colourless needles, m.p. 166/167°C. (Lit. 167°C).

Yield = 1.5g (33%).

Analysis: $C_{13}H_{13}ON$	Requires	Found
% Carbon	78.38	78.03
% Hydrogen	6.53	6.86
% Nitrogen	7.03	7.09

Reduction of 1-Keto-8-methyltetrahydrocarbazole to 8-Methyltetrahydrocarbazole.

A solution of the ketone (0.75g) was added in portions to a boiling mixture of water and concentrated hydrochloric acid, to which zinc amalgam had been added. The experimental conditions were the same as in the reduction of 1-ketotetrahydrocarbazole (p. 54). A few drops of concentrated hydrochloric acid were added after the addition of each portion of the ketone solution.

After/

After 3 hours further boiling the liquid was decanted, and water was added, bringing down a white solid. Since the solid did not readily coagulate, so that filtration was difficult, it was extracted twice with ether. The ethereal solution was dried over anhydrous sodium sulphate and evaporated to dryness. A pale brown residue was obtained. Recrystallisation from light petroleum (60/80°C) gave a colourless solid of indefinite crystalline form, melting with decomposition at 122°C. See p. 119.

Yield = 0.55g.

Analysis: $C_{13}H_{15}N$	Requires	Found
% Carbon	84.31	72.63
% Hydrogen	8.11	7.46

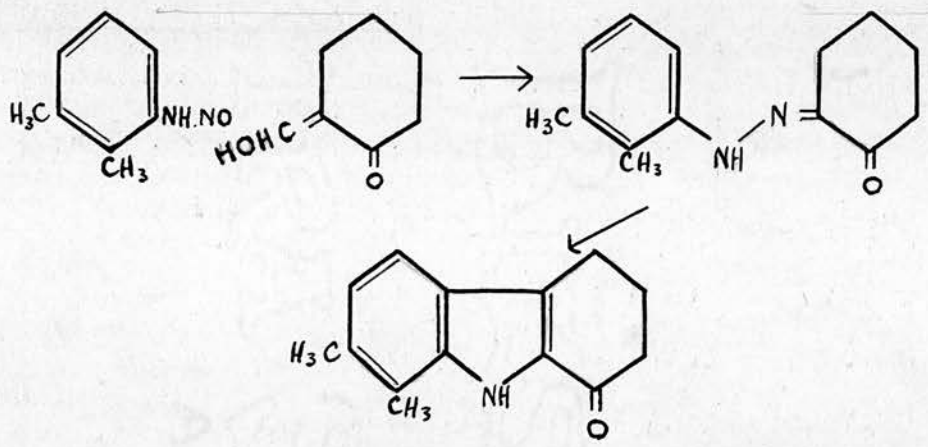
The previous experiment was repeated under identical conditions. On this occasion evaporation of the ethereal solution gave an almost colourless residue. This crystallised easily from aqueous alcohol, giving colourless plates, m.p. 97/9°C (Lit. 97/8°C). A mixed melting-point with an authentic sample of 8-methyltetrahydrocarbazole showed no depression.

Yield = 0.6g (87%)

Analysis: $C_{13}H_{15}N$	Requires	Found
% Carbon	84.31	83.98
% Hydrogen	8.11	8.19

Preparation/

Preparation of the Mono-2:3-dimethylphenylhydrazone of Cyclohexane-1:2-dione, and of 7:8-Dimethyl-1-ketotetrahydrocarbazole



Coffey's synthesis was applied to o-3-xylidine. The amine (10g), after diazotisation and neutralisation, reacted with oxymethylene cyclohexanone to give the mono-2:3-dimethylphenylhydrazone of cyclohexane-1:2-dione. The final product separated slowly as a very fine yellow precipitate which, on continued stirring, coagulated and darkened slightly. It was filtered, dried and recrystallised from alcohol. Golden-brown prisms were obtained, m.p. 87/90°C.

Yield = 10g (53%)

A sample was recrystallised from light petroleum (60/80°C) giving deep red prisms, m.p. 89/91°C. The hydrazone was very soluble in hot glacial acetic acid and hot benzene, and moderately soluble in the cold.

Analysis/

Analysis:	$C_{14}H_{18}ON_2$	Requires	Found
	% Carbon	73.05	72.33
	% Hydrogen	7.83	7.85

The dimethylphenylhydrazone (5g) was boiled in the usual manner with glacial acetic acid and concentrated hydrochloric acid, and poured into water. The grey solid which was precipitated was filtered and dried.

A portion was dissolved in the minimum of cold benzene and purification by chromatographing in a small column attempted (alumina 6 x 1 inch). Since the ketone was strongly adsorbed in the column, moving downwards very slowly, the attempt was abandoned. The crude product was recrystallised from benzene (charcoal). Pale yellow needles separated which on further crystallisation from alcohol became colourless. M.p. 200/201°C.

Yield 2.0g (46%)

Analysis:	$C_{14}H_{15}ON$	Requires	Found
	% Carbon	79.51	78.38
	% Hydrogen	7.10	7.02

<u>Attempted reduction of 1-Keto-7:8-dimethyltetrahydrocarbazole to 7:8-Dimethyltetrahydrocarbazole.</u>

The ketone (0.75g) was dissolved in the minimum of alcohol and reduction attempted in the usual fashion by the method of Clemmensen. After

boiling/

boiling, the alcoholic solution was poured into water, and the resulting white precipitate extracted twice with ether. The ethereal solution, which soon began to exhibit a green fluorescence, was evaporated, giving a colourless crystalline solid, m.p. 80/2°C.

Yield = 0.5g (72%)

Analysis: $C_{14}H_{17}N$	Requires	Found
% Carbon	84.41	82.41
% Hydrogen	8.54	8.31

A picrate of the substance crystallised from benzene as chocolate needles, m.p. 155/7°C.

Three portions of the crude solid were recrystallised from light petroleum.

The first, on recrystallisation from light petroleum (40/60°C), to which a few drops of benzene were added, gave colourless crystals (A) of indefinite shape, separating from solution over a period of hours, m.p. 106/7°C, with slight decomposition on melting.

Analysis: Found - % C = 72.83; % H = 7.23

The second crystallised very slowly from the same solvent (charcoal) as a colourless amorphous solid (B). It melted with vigorous decomposition at 115°C.

Analysis: Found - % C = 72.23; % H = 7.27
% N = 7.46

The mother-liquor on evaporation yielded a further quantity of the same substance.

A third sample of the crude compound was recrystallised from light petroleum (80/100°C) giving colourless plates (C) of 7:8-dimethyltetrahydrocarbazole, m.p. 84/86°C.

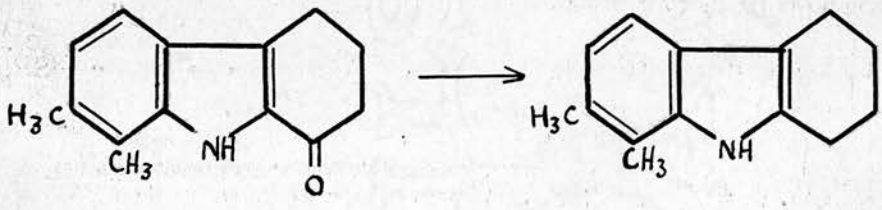
Analysis: $C_{14}H_{17}N$	Requires	Found
% Carbon	84.41	83.89
% Hydrogen	8.54	8.81
% Nitrogen	7.03	7.23

The crystals slowly became yellow in air.

A picrate of this compound was made in benzene solution. Lustrous chocolate needles were obtained, m.p. 157/8°C.

Analysis of Picrate:

$C_{20}H_{20}O_7N_4$	Requires	Found
% Nitrogen	13.1	13.2



When the mother liquor from the recrystallisation which yielded C was evaporated, a small quantity of a white amorphous solid was obtained. Recrystallisation of this was attempted from light petroleum (80/100°C), but it would not dissolve even when boiled with 3-4 times the original volume of solvent. It was filtered, and was found to melt/

melt with decomposition at 115°C. When mixed with the sample B, the melting-point as before was 115°C with vigorous decomposition. The amorphous solid was fairly soluble in alcohol to give a strong green fluorescence, but an attempt to recrystallise from this solvent was unsuccessful.

Preparation of 1:2-Dimethylcarbazole.

7:8-Dimethyltetrahydrocarbazole (0.98g), chloranil (2.61g) and 30 ml sulphur-free xylene were boiled gently for twenty-four hours. On standing overnight most of the tetrachlorohydroquinone formed had separated, and was filtered. The mother liquor and washings were diluted with an equal volume of ether and washed thoroughly with 4% aqueous caustic potash solution to remove any remaining hydroquinone. The solution was washed with water, dried for several hours over anhydrous sodium sulphate and reduced to small volume under reduced pressure. On standing, the solution, which had a very strong blue fluorescenee, deposited a dark/

dark violet solid, which crystallised from light petroleum (100/120°C) (charcoal), in colourless prisms. M.p. 147/8°C.

Yield of 1:2-dimethylcarbazole = 0.4g (42%).

Analysis: $C_{14}H_{13}N$	Requires	Found
% Carbon	86.16	85.53
% Hydrogen	6.67	6.88

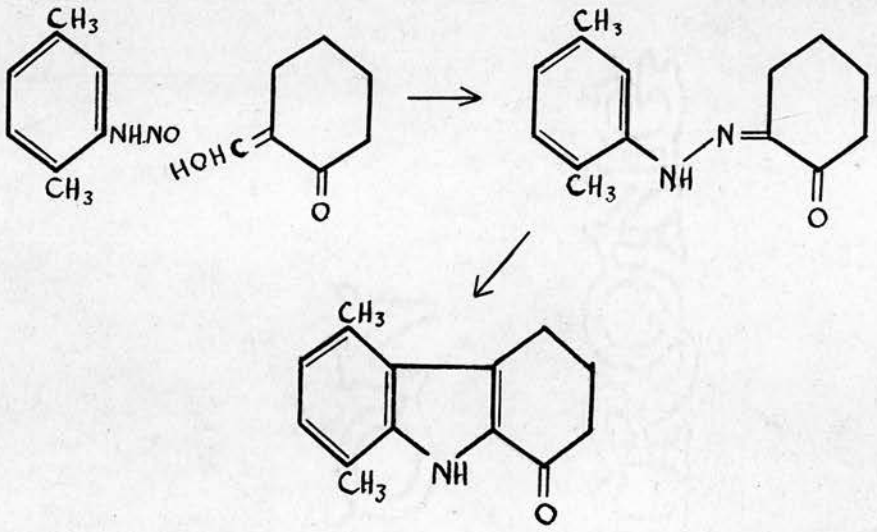
A picrate was obtained in benzene solution giving bright orange-red needles, which were recrystallised from benzene. M.p. 162/3°C.

Analysis of Picrate:

$C_{20}H_{16}O_7N_4$	Requires	Found
% Nitrogen	13.2	13.2

Colour Test: With concentrated sulphuric acid 1:2-dimethylcarbazole gave no colour, but the further addition of one drop of concentrated nitric acid produced a deep blue-green colour.

Preparation of the Mono-2:5-dimethylphenylhydrazone of Cyclohexane-1:2-dione and its subsequent cyclisation to form 5:8-Dimethyl-1-ketotetrahydrocarbazole.



By the usual method, p-xylidine (15g) was diazotised and neutralised with dilute caustic soda at 0°C. On the slow addition of oxymethylene cyclohexanone, an amber oil was formed, which solidified on standing overnight to give an orange-red solid. This was filtered, dried and recrystallised from methyl alcohol. The dimethylphenylhydrazone was obtained as yellow plates, m.p. 71/73°C.

Yield = 16g, (56%)

The compound was fairly soluble in benzene, light petroleum and glacial acetic acid.

Analysis: $C_{14}H_{18}ON_2$	Requires	Found
% Carbon	73.05	72.56
% Hydrogen	7.83	7.83

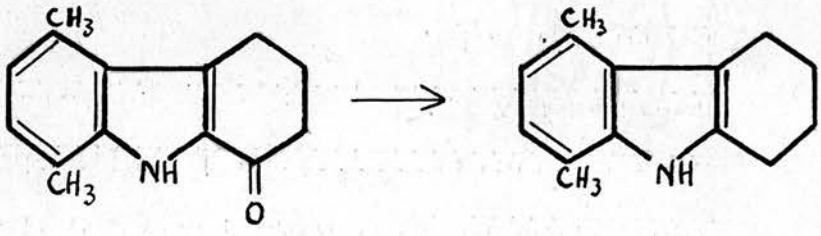
When/

When this dimethylphenylhydrazone (5g) was boiled under reflux with glacial acetic acid and concentrated hydrochloric acid and poured into water, a grey solid separated out; it was filtered, dried and recrystallised from benzene (charcoal). A white microcrystalline solid was obtained. Further recrystallisation from a mixture of benzene and light petroleum (100/120°C) produced colourless needles, m.p. 221/3°C. From methyl alcohol colourless prisms were obtained, m.p. 224/5°C. The ketone was very soluble in hot benzene, alcohol and glacial acetic acid, slightly soluble in light petroleum.

The yield of pure 5:8-dimethylketotetrahydrocarbazole was 2.5g (54%).

Analysis: $C_{14}H_{15}ON$	Requires	Found
% Carbon	79.51	78.61
% Hydrogen	7.10	7.19

Reduction of 5:8-Dimethyl-1-ketotetrahydrocarbazole.



The/

The reduction of the ketone (1.5g) was accomplished in alcoholic solution by the usual method. On pouring into water, after boiling, a milky-white solid was precipitated. The precipitate, which did not readily coagulate, was extracted several times with ether. The extract was dried over anhydrous sodium sulphate. When evaporated a white residue remained, which was extremely soluble in cold alcohol and benzene and moderately so in light petroleum. Recrystallisation from aqueous methyl alcohol or light petroleum (80/100°C) gave pure 5:8-dimethyltetrahydrocarbazole as colourless prisms, m.p. 88/9°C.

Yield = 1.37g (98%).

Analysis: $C_{14}H_{17}N$	Requires	Found
% Carbon	84.41	84.00
% Hydrogen	8.54	8.00
% Nitrogen	7.03	6.95

A picrate of 5:8-dimethyltetrahydrocarbazole was made in methyl alcohol. Chocolate-brown needles were obtained, but not recrystallised. m.p.?

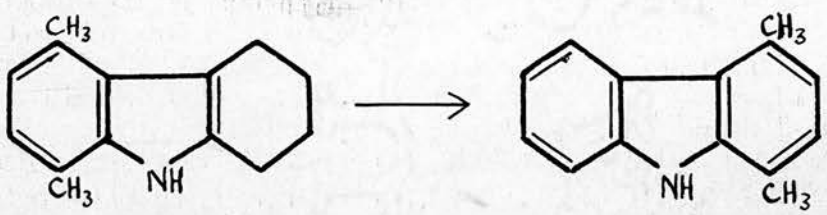
Analysis of Picrate:

$C_{20}H_{20}O_7N_4$	Requires	Found
% Nitrogen	13.1	13.1

The mother-liquor from which 5:8-dimethyltetrahydrocarbazole was crystallised (light petroleum) on evaporation left a white residue, melting with decomposition/

decomposition at 128°C. The solution of this substance in ether, alcohol and benzene, had a bright green fluorescence.

Preparation of 1:4-Dimethylcarbazole by the dehydrogenation (chloranil) of 5:8-Dimethyl-tetrahydrocarbazole.



5:8-Dimethyltetrahydrocarbazole (1.18g) chloranil (3.14g) and 20 ml. sulphur-free xylene were boiled gently for 24 hours, and allowed to cool. After the same procedure as in the case of 7:8-dimethyltetrahydrocarbazole (p. 68) the blue fluorescent solution was evaporated to small volume under reduced pressure. No solid separated out on standing, but a black tarry substance was obtained. This was dissolved in a few ml. benzene and run through a short column (alumina 3 x 1 inch). A deep blue band remained at the top of the column. This had no fluorescence. Below this there appeared a very pale violet band with a bright blue fluorescence, which quickly moved down. The eluate from this band was evaporated, yielding a colourless/

colourless oil, which was then dissolved in the minimum of light petroleum to which a drop of benzene had been added. Colourless crystals separated in the form of little rosettes of needles, m.p. 79/82°C.

Yield of 1:4-dimethylcarbazole = 0.6g (52%).

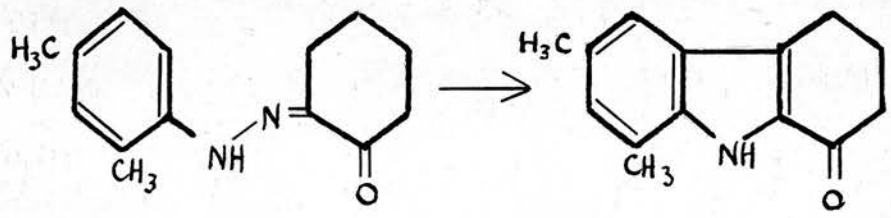
Analysis: $C_{14}H_{13}N$	Requires	Found
% Carbon	86.16	85.3
% Hydrogen	6.67	6.48

A picrate of 1:4-dimethylcarbazole was formed in benzene solution with a little light petroleum added (60/80°C). Lustrous bright red needles were obtained, m.p. 142/3°C.

Analysis: $C_{20}H_{16}O_7N_4$	Requires	Found
% Nitrogen	13.2	12.8

Colour Test: No colour was obtained by the addition of concentrated sulphuric acid to a trace of 1:4-dimethylcarbazole, but the further addition of one drop concentrated nitric acid produced a pale green colour, slowly turning amber.

Preparation of the Mono-2:4-dimethylphenylhydrazone of Cyclohexane-1:2-dione, and its conversion to 6:8-Dimethyl-1-ketotetrahydrocarbazole.



When/

When m-4-xylidine (18g) was diazotised with sodium nitrite in the presence of excess hydrochloric acid, the diazo solution neutralised with dilute caustic soda, and oxymethylene cyclohexanone added (according to Coffey's method) an oil separated, very slowly solidifying to form a dark brown coagulated mass. The solid was filtered and recrystallised from alcohol.

Yield of the dimethylphenylhydrazone = 19g (55%).

From light petroleum dark red prisms crystallised; from alcohol, orange rhombic prisms. M.p. 81/3°C.

Analysis: $C_{14}H_{18}ON_2$	Requires	Found
% Carbon	73.05	72.20
% Hydrogen	7.83	7.71

The mono-2:4-dimethylphenylhydrazone of cyclohexane-1:2-dione (12g) was boiled with glacial acetic acid and concentrated hydrochloric acid for 30 minutes and poured into water. A brown oil immediately separated which on stirring soon solidified to give a dark brown solid. It was filtered, dried and boiled in benzene solution (charcoal). The solution was filtered and reduced in volume. When cool, a pale yellow solid separated, and was recrystallised from methyl alcohol to form colourless prisms, m.p. 191/192°C.

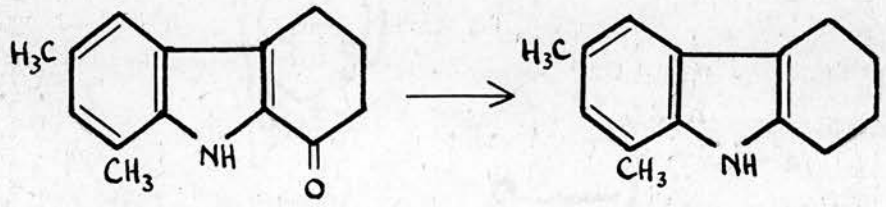
Yield/

Yield of the pure 6:8-dimethylketotetrahydrocarbazole = 5g (45%).

It was very soluble in hot benzene, alcohol and glacial acetic acid.

Analysis: $C_{14}H_{15}ON$	Requires	Found
% Carbon	79.51	78.69
% Hydrogen	7.10	6.92

Preparation of 6:8-Dimethyltetrahydrocarbazole.



6:8-Dimethylketotetrahydrocarbazole (1.5g) was reduced as before in alcoholic solution. After the usual period of boiling, the liquid was poured into water bringing down a fine white solid. It was extracted with ether and the extract dried and evaporated. Colourless prisms separated. Recrystallisation from light petroleum yielded colourless prisms, m.p. 92/4°C.

Yield of 6:8-dimethyltetrahydrocarbazole = 1g (72%)

Analysis: $C_{14}H_{17}N$	Requires	Found
% Carbon	84.41	83.68
% Hydrogen	8.54	8.58

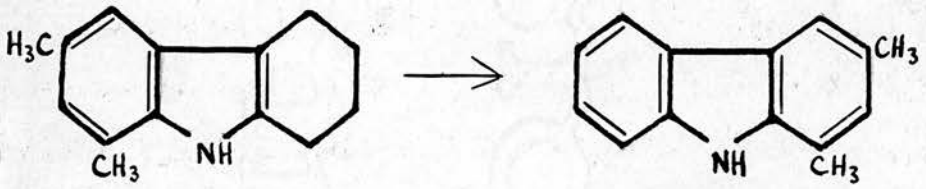
6:8/

6:8-Dimethyltetrahydrocarbazole formed a picrate in benzene solution. The brown solid formed crystallised from benzene in lustrous chocolate-brown needles, meltingat 162/3°C. They soon, however, showed signs of decomposition.

Analysis: $C_{20}H_{20}O_7N_4$	Requires	Found
% Nitrogen	13.1	12.6

On heating a dilute solution of 6:8-dimethyltetrahydrocarbazole in light petroleum and a few drops of benzene, and cooling, colourless prisms slowly separated. These were filtered, heated with a little benzene, in which they were not very soluble, and filtered once more. M.p. (with decomposition) 130°C. Their solution in ether, alcohol and benzene fluoresced a bright green.

Preparation of 1:3-Dimethylcarbazole.



6:8-Dimethyltetrahydrocarbazole (0.8g) was dehydrogenated by boiling with chloranil in xylene (sulphur-free) solution, in the usual manner; on cooling, a solid separated whose appearance suggested that some of the carbazole had separated as well as tetrachlorohydroquinone. Ether was added/

added, bringing all the solid into solution; the liquid was washed with 4% aquepus caustic potash and water, dried over anhydrous sodium sulphate and reduced to very small volume under reduced pressure. The dark solution, which had a bright blue fluorescence, did not deposit any solid on standing overnight. It was run through a small column (alumina 3 x 1 inch) and developed with light petroleum (100/120°C). As in the case of 1:4-dimethylcarbazole, a dark blue band remained at the top of the column, while a pale violet (blue fluorescant) band moved quickly down. The eluate from this portion yielded on evaporation a white solid which crystallised from light petroleum (40/60°C). as colourless prisms, m.p. 94°C (Lit. 95°).

Yield of pure 1:3-dimethylcarbazole = 0.2g (26%).

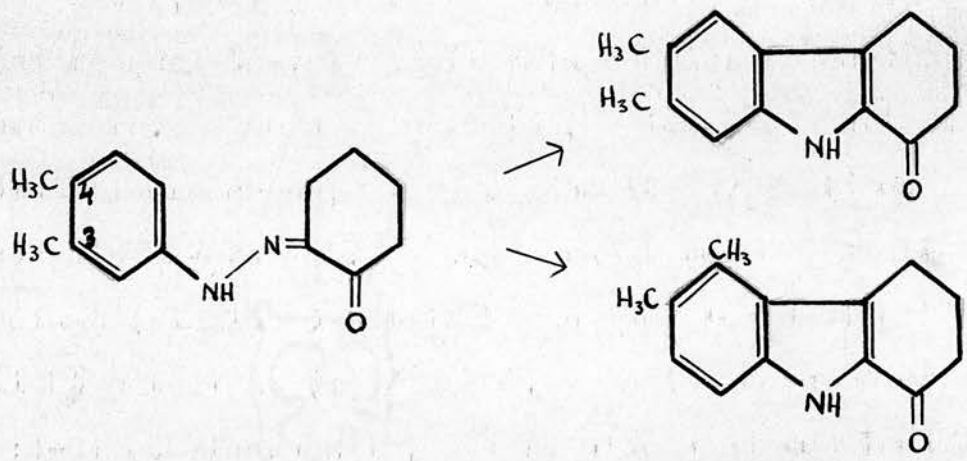
Analysis: $C_{14}H_{13}N$	Requires	Found
% Carbon	86.16	85.06
% Hydrogen	6.69	6.77

Colour Test: With concentrated sulphuric acid, a trace of 1:3-dimethylcarbazole gave a pale green colour. On the further addition of one drop of concentrated nitric acid, a deep blue-green appeared.

Picrate of 1:3-methylcarbazole: Bright red needles from benzene, m.p. 186/7°C (Lit. 188.5°C)

Preparation/

Preparation of the Mono-3:4-Dimethylphenylhydrazone of Cyclohexane-1:2-dione and its subsequent cyclisation.



As in the case of other xylidines, o-4-xylidine (10g) was diazotised, the diazo solution neutralised, and oxymethylene cyclohexanone added with vigorous stirring, the whole reaction being carried out below 0°. The solid which separated, bright yellow in colour, quickly coagulated and turned orange. Recrystallisation from glacial acetic acid or alcohol produced yellow plates, m.p. 163/5°C. The solid was sparingly soluble in hot alcohol and fairly soluble in boiling glacial acetic acid.

Yield of the dimethylphenylhydrazone = 14g (74%)

Analysis: $C_{14}H_{18}ON_2$	Requires	Found
% Carbon	73.05	72.00
% Hydrogen	7.83	7.76

The hydrazone (10g) was as before boiled with glacial acetic acid and concentrated hydrochloric acid/

acid, and poured into water, when a brown solid was precipitated. The solid was dissolved in boiling benzene (charcoal), the solution filtered, and evaporated. A very pale brown residue was left, in 6.5g yield. M.p. 170/178°C. On fractional crystallisation of a portion of this solid (1.0g) from benzene, a slight separation was noted. The first several fractions to crystallise had a melting-point of about 170/176°C. The mother liquor was evaporated, leaving a residue, m.p. 182/9°C. A further crystallisation of this residue from benzene did not alter the melting point.

Another portion of the supposed mixture (5.0g) was extracted twice in the cold with ether, and an examination carried out of the extracts (A) and (B), and the residue (C).

The first extract, (A), when evaporated yielded a solid (0.3g), melting at 192/7°C, which on crystallisation from methyl alcohol gave very pale brown elongated prisms, m.p. 195/7°C. A further recrystallisation from a mixture of alcohol and glacial acetic acid raised the melting-point to 200/1°C, but reduced the yield to 0.04g.

From the second extract, (B), was obtained a solid (0.5g), m.p. 175/81°C, and from the residue, (C), a solid melting, on recrystallisation from alcohol, at 172/5°C. The latter (3.0g) was dissolved/

dissolved in the minimum of cold benzene and chromatographed (alumina 16 x 1½ inch). After 24 hours a separation was observed into two yellow bands (Fig. 5). The top band, light yellow, had a faint light green fluorescence, while the bottom darker yellow band fluoresced to a slightly greater extent, again light green. The column was dried, cut into portions and extracted with alcohol.

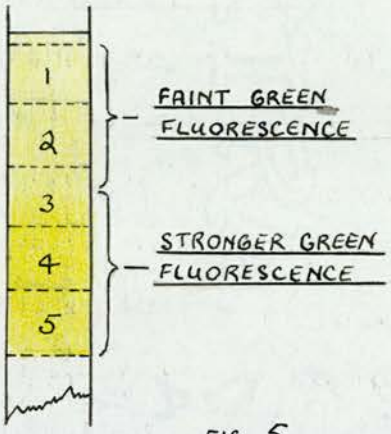


FIG. 5

Portions 1 and 2 each gave a solid melting at 174/6°C, yield 1.4g. Portion 3 when evaporated yielded a solid m.p. 172/6°C. The fourth portion - m.p. 188/94°C; the fifth portion - m.p. 189/94°C.

The solid, m.p. 174/6°C, was recrystallised from benzene; yellow compact prisms were obtained, m.p. 176/8°C.

Analysis: $C_{14}H_{15}ON$	Requires	Found
% Carbon	79.51	78.56
% Hydrogen	7.10	7.15
% Nitrogen	6.57	6.46

Each of the solids 4 and 5 on recrystallising from a mixture of alcohol and glacial acetic acid gave long yellow prisms, m.p. 200/201°C, which were/

were shown by mixed melting-point to be identical with the compound obtained from ether extract (A). Although the combined yields of solids 4 and 5 from the column were 0.8g, that of the purified substance was only 0.3g.

Analysis: $C_{14}H_{15}ON$	Requires	Found
% Carbon	79.51	78.63
% Hydrogen	7.10	7.20
% Nitrogen	6.57	6.71

It was noticed that the yellow compact prisms from portions 1 and 2 of the column, m.p. 176/8°C, when recrystallised slowly from a mixture of acetone and glacial acetic acid (2:1) separated out as a mixture of elongated and compact prisms. A solution was made with that solvent mixture, the solid being dissolved in a little more than the minimum volume required, and allowed to cool very slowly in a stoppered vessel without shaking. After two days the solution was filtered and the crystals separated mechanically into long and compact prisms melting at 196/8°C and 175/185°C respectively. Recrystallisation of the long prisms from the same solvent gave a compound, m.p. 201°C, identical to that from ether extract (A) (mixed melting-point). The compact prisms on recrystallisation again gave elongated and compact prisms, which were again separated mechanically. The

former/

former were identified with (A) once more, while the latter now melted at 205/223°C. Three re-crystallisations of these compact prisms from acetone-glacial acetic acid gave crystals, m.p. 225/7°C. Further recrystallisation did not raise the melting-point.

Analysis: $C_{14}H_{15}ON$	Requires	Found
% Carbon	79.51	78.45
% Hydrogen	7.10	7.10

A mixture of equal quantities of the two ketones, melting at 201°C and 225/7°C, melted at 173/6°C.

Reduction of the Dimethyl-1-ketotetrahydrocarbazole m.p. 201°C.

The ketone (0.4g) was dissolved in alcohol and reduced with zinc amalgam and hydrochloric acid as before. When the solution was poured into water a white solid separated. This was filtered, dried and recrystallised from light petroleum, m.p. 119/130°C.

Yield = 0.29g (78%)

Analysis: $C_{14}H_{17}N$	Requires	Found
% Carbon	84.41	84.09
% Hydrogen	8.54	8.61
% Nitrogen	7.03	7.00

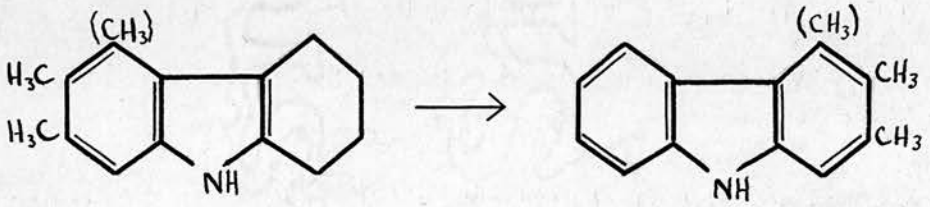
A/

A picrate (in benzene) came down as chocolate needles, m.p. 168°C.

Analysis: $C_{20}H_{20}O_7N_4$	Requires	Found
% Nitrogen	13.1	13.0

The compound is either 5:6- or 6:7-dimethyltetrahydrocarbazole.

<u>The Dehydrogenation of 6:7- (or 5:6-) Dimethyltetrahydrocarbazole</u>.



The dimethyltetrahydrocarbazole (0.25g), chloranil (0.67g) and 10 ml. sulphur-free xylene were boiled gently for 24 hours. After the usual treatment the solution was reduced to small volume under reduced pressure, and since it was dark blue in colour (bright blue fluorescence) it was run through a small column of alumina (2 x 1 inch), which removed a dark blue impurity. The solution after chromatographing was almost colourless, with a bright blue fluorescence. On evaporation a colourless solid was obtained. Crude yield = 0.15g, m.p. 245/50°C. Recrystallisation from benzene gave colourless plates, m.p. 250/2°C.

Yield/

Yield of 2:3- (or 3:4-) dimethylcarbazole = 0.1g (42%).

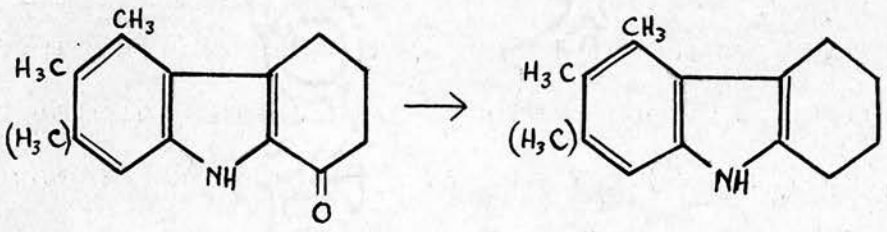
Analysis: $C_{14}H_{13}N$	Requires	Found
% Carbon	86.16	86.20
% Hydrogen	6.67	6.86

A picrate separated from benzene solution as red needles, m.p. 166/8°C. It soon showed signs of decomposition.

Analysis: $C_{20}H_{16}O_7N_4$	Requires	Found
% Nitrogen	13.2	12.6

Colour Test: With concentrated sulphuric acid this dimethylcarbazole gave a grass green colouration. The addition of one drop of concentrated nitric acid caused a darkening to olive green.

Reduction of the Dimethylketotetrahydrocarbazole m.p. 225/7°C.



5:6- (or 6:7) Dimethyl-1-ketotetrahydrocarbazole (0.2g) was dissolved in alcohol, and reduction attempted as before. On pouring into water, no solid separated. Caustic soda (aqueous) was added in excess, and the mixture extracted twice with ether. The extract was dried over anhydrous/

anhydrous sodium sulphate, and evaporated, leaving a brown oil. This could not be solidified by attempted crystallisation from alcohol, benzene or light petroleum, or by trituration with these solvents.

The oil assumed to contain 5:6- (or 6:7-) dimethyltetrahydrocarbazole (0.15g), was boiled with chloranil and sulphur-free xylene for 24 hours. The blue fluorescent liquid, after the usual treatment, was reduced to small volume and run through a short column (alumina 2 x 1 inch). The light blue liquid obtained, with a bright blue fluorescence, yielded an evaporation a white solid recrystallised from benzene to give colourless prisms, m.p. 159/60°C.

Yield = 0.06g (43%).

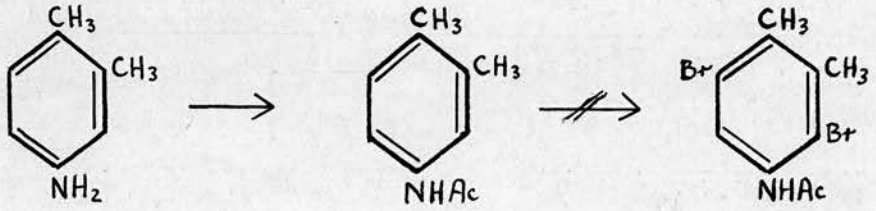
A mixed melting point with 3:4-dimethylcarbazole (see p. 94) (m.p. 159/60°C) was not depressed.

A picrate was made in methyl alcohol. Bright red needles were obtained, but showed signs of decomposition very quickly.

Analysis: $C_{20}H_{16}O_7N_4$	Requires	Found
% Nitrogen	13.2	14.3

The/

Attempted preparation of 3:6-Dibromoacetyl-o-4-xylidine (Jaeger and Blanksma, Rec. trav. chim. 1906, 25, 354).



Commercial o-4-xylidine (20g) was dissolved in a mixture of 15 ml glacial acetic acid and 15 ml acetic anhydride, and boiled under reflux for 30 minutes. It was poured into water, precipitating a white solid, the monoacetyl derivative of o-4-xylidine. Recrystallisation from aqueous alcohol gave colourless needles, m.p. 99°C (Lit.)

The acetyl derivative was dissolved in 25 ml glacial acetic acid and to the solution 54g bromine was added dropwise with stirring. Stirring was continued for an hour after all the bromine had been added. The dark red solution was poured into ice and water, when a brown liquid settled to the bottom. This was separated and triturated with a mixture of equal volumes of glacial acetic acid and alcohol. Brown prisms separated on standing; recrystallisation from alcohol (twice) yielded colourless prisms, m.p. 165/6°C.

Yield = 15g.

Analysis/

Analysis: Found - % Br. 32.3; % N. 5.5.

$C_{10}H_{11}ONBr_2$ Requires % Br. 53.1 % N 4.7

$C_{10}H_{12}ONBr$ Requires % Br. 33.0 % N 5.8

The compound is thus a monobromo derivative.

The experiment was repeated on a smaller scale, using excess bromine. o-4-Xylidine (0.5g) was acetylated, and the acetyl derivative dissolved in 3 ml. glacial acetic acid. Bromine (2.0g) was added with vigorous stirring. The solution was left with stirring overnight, heated to about 60°C, and an equal volume of alcohol added. When cool, long prisms separated which were recrystallised from alcohol, m.p. 164/5°C. A mixed melting-point carried out with the above bromo compound showed no depression.

Hydrolysis of Monobromoacetyl-o-4-xylidine.

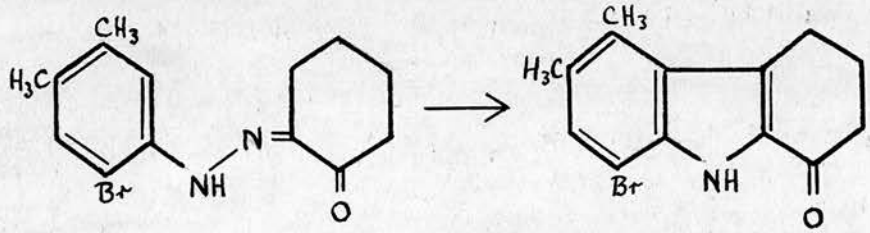
The above acetyl derivative was boiled for 30 minutes with 70% sulphuric acid (by weight), allowed to cool, and carefully diluted with water. A white solid crystallised out in the form of plates. This, the amine sulphate, was treated with caustic soda yielding a solid which crystallised from light petroleum (80/100°) in colourless plates, m.p. 85/7°C.

Analysis: Found - % Br. 41.0

$C_8H_{10}NBr$ Requires % Br. 40.0

Preparation/

Preparation of the Mono-2-bromo-4:5-dimethylphenylhydrazone of Cyclohexane-1:2-dione, and its ring-closure to form 8-Bromo-5:6-dimethyl-1-ketotetrahydrocarbazole.



The sulphate of 5-bromo-o-4-xylidine (12g) was suspended in sulphuric acid (20 ml. concentrated sulphuric acid to which had been added carefully 150 ml. water) and diazotised with a solution of sodium nitrite (8 g) in 30 ml. water. The diazo solution wasneutralised with dilute caustic soda, and on the addition of oxymethylene cyclohexanone an orange solid at once separated. This, the mono-2-bromo-4:5-dimethylphenylhydrazone of cyclohexane-1:2-dione, was filtered and recrystallised from alcohol to which a little glacial acetic acid had been added. It came down in good yield as orange prisms, m.p. 154/6°C. Recrystallisation from light petroleum gave deep red prisms.

Analysis: $C_{14}H_{17}ON_2Br$	Requires	Found
% Bromine	25.9	26.4
% Nitrogen	9.1	8.9

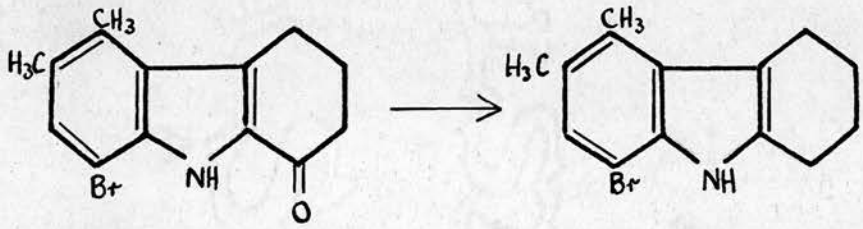
On boiling the hydrazone in the usual manner/

manner with concentrated hydrochloric acid and glacial acetic acid, and pouring into water, a dark brown solid separated. The yield of crude product was 10g. Recrystallisation was carried out from benzene (charcoal) and then from a mixture of alcohol and acetic acid. Orange prisms were obtained, m.p. 209/11°C. A further recrystallisation from benzene gave colourless prisms, m.p. 211°C.

Yield = 5g.

Analysis: $C_{14}H_{14}ONBr$	Requires	Found
% Bromine	27.4	27.6
% Nitrogen	4.8	4.9

Reduction of 8-Bromo-5:6-dimethyl-1-ketotetrahydrocarbazole.



The ketone (3.4g) was dissolved in alcohol and reduction carried out with zinc amalgam and hydrochloric acid. The filtrate was poured into water, and the tetrahydrocarbazole extracted with ether. A white solid was obtained which crystallised from light petroleum in colourless prisms, m.p. 94/5°C.

Yield of 8-Bromo-5:6-dimethyltetrahydrocarbazole = 2.2g (74%).

Analysis/

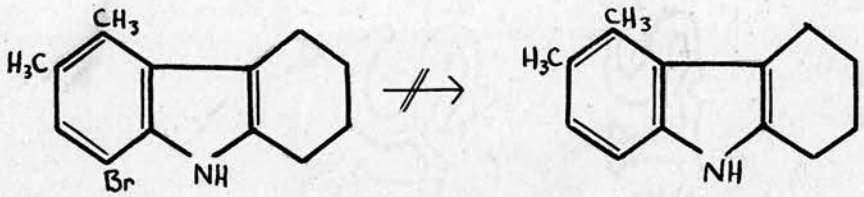
Analysis:	$C_{14}H_{16}NBr$	Requires	Found
	% Bromine	28.8	29.5

Further recrystallisation from alcohol raised the melting-point to 101°C.

8-Bromo-5:6-dimethyltetrahydrocarbazole formed a picrate which crystallised in benzene solution as lustrous reddish-brown needles, m.p. 173/4°C.

Analysis:	$C_{20}H_{19}O_7N_4Br$	Requires	Found
	% Nitrogen	11.0	11.0

<u>The attempted dehalogenation with Raney nickel of 8-Bromo-5:6-dimethyltetrahydrocarbazole</u>.

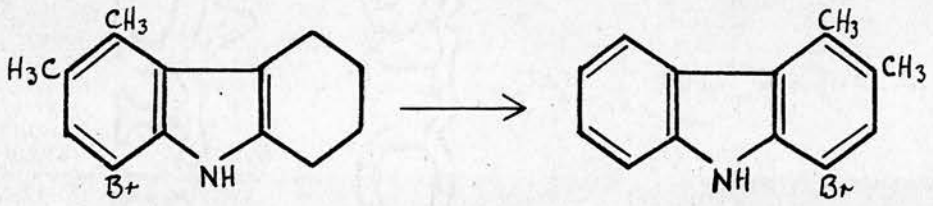


The bromo-tetrahydrocarbazole (1g), 30 ml. of a 10% aqueous caustic soda solution and 25 ml. alcoholic caustic soda were boiled under reflux on the water-bath, and 3g of an aluminium nickel alloy, finely powdered, added in small portions over a period of 45 minutes. Boiling was continued for a further period of 2 hours. The catalyst was filtered off, and the filtrate treated with water and extracted with ether. The ether extract was washed thoroughly with dilute hydrochloric acid, then with water/

water, and dried over anhydrous sodium sulphate. When evaporated a white solid was left which crystallised from light petroleum in colourless rhombic prisms, m.p. 99/100°C. A mixed melting-point with 8-bromo-5:6-dimethyltetrahydrocarbazole showed no depression.

This attempted reduction was repeated with a similar result.

Preparation of 1-Bromo-3:4-dimethylcarbazole.



8-Bromo-5:6-dimethyltetrahydrocarbazole (1.13g), chloranil (1.81g) and 20 ml. sulphur-free xylene were boiled gently for 24 hours. After the usual treatment the solution was evaporated to small volume and allowed to stand. No solid separated, and since it was very dark, the solution was diluted with a little benzene to give a total volume of 4 mls, and purified by chromatography (alumina 3 x 1 inch). A dark brown and a blue band were strongly adsorbed, while a very pale yellow band moved down fairly quickly. Three

30/

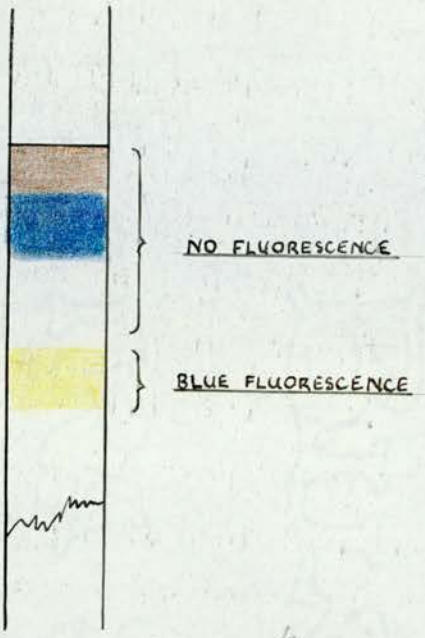


FIG. 6

30 ml. portions of eluate from this band each yielded a colourless solid, m.p. about 90°C. Total yield 0.8g. Recrystallised from light petroleum (80/100°C) the solid separated as colourless prisms, m.p. 98/9°C.

Analysis:	$C_{14}H_{12}NBr$	Requires	Found
	% Bromine	29.2	29.3

Yield of pure 1-bromo-3:4-dimethylcarbazole = 0.6g (50%).

A mixed melting-point with the tetrahydrocarbazole showed a comsiderable depression (m.p. 60/80°C).

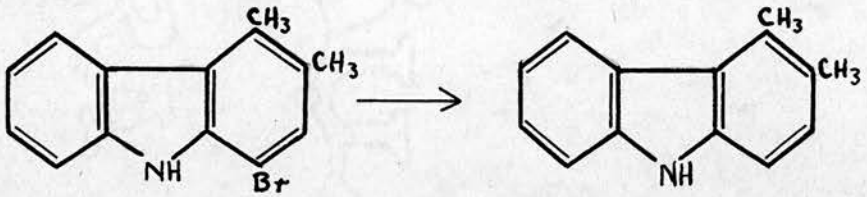
A picrate of 1-bromo-3:4-dimethylcarbazole crystallised from benzene as bright red needles, m.p. 163°C.

Analysis:	$C_{20}H_{15}O_7N_4Br$	Requires	Found
	% Nitrogen	11.1	10.3

Colour test: 1-Bromo-3:4-dimethylcarbazole gave a greenish/

greenish-brown colour with concentrated sulphuric acid, and on the addition of one drop of concentrated nitric acid the colour became amber.

Preparation of 3:4-Dimethylcarbazole by debromination of 1-Bromo-3:4-dimethylcarbazole.



The bromo compound (0.33g), red phosphorus (0.2g) and hydriodic acid (5 ml.) were boiled for 4 hours and poured into aqueous potassium iodide solution. The brown oily liquid, after standing for an hour, was extracted with ether and the extract shaken in turn with caustic soda, water, sodium thiosulphate and water. It was then dried over anhydrous sodium sulphate and evaporated to dryness, leaving a brown solid. The solid was dissolved in a little benzene and run through a small column (3 x 1 inch), which retained the brown colour as a band at the top, while a colourless band with a bright blue fluorescence moved quickly down. The eluate of this band yielded a pale yellow solid melting about 150°C.

The solid was recrystallised from light petroleum/

petroleum (80/100°) coming down as colourless prisms, m.p. 159/60°C.

Analysis: $C_{14}H_{13}N$	Requires	Found
% Carbon	86.16	85.78
% Hydrogen	6.67	7.06

Yield of pure 3:4-dimethylcarbazole = 0.1g (43%).

Colour Test: With concentrated sulphuric acid 3:4-dimethylcarbazole gave a pale green colour. The addition of a drop of concentrated nitric acid changed the colour to amber.

Preparation of 2:3-Dimethylphenylhydrazine

(Franzen, Onsager & Faerden, J. Prakt. Chem. 1918, 344, 97).

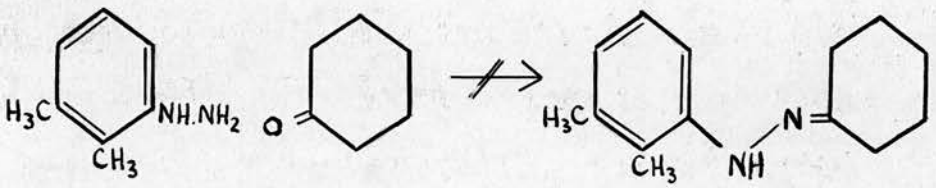
Claims yield of 45·5%. Free hydrazine stated to decompose readily

o-Xylidine (5g) was dissolved in hydrochloric acid, cooled to -7°C, and diazotised. The diazo solution was poured slowly with cooling into a solution of stannous chloride in concentrated hydrochloric acid. The double tin salt which separated was decomposed with caustic soda, and the 2:3-dimethylphenylhydrazine extracted with ether. On the addition of alcoholic hydrochloric acid, the hydrochloride separated as colourless plates. M.p. 207°C.

Yield = 2g (36%)

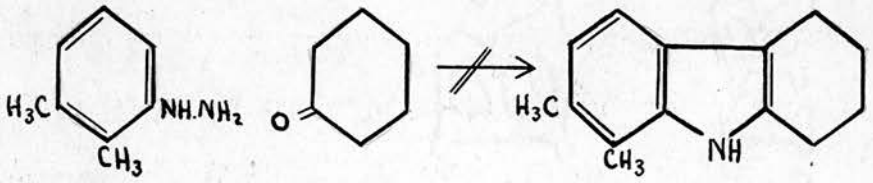
Attempted/

Attempted preparation of the 2:3-Dimethylphenylhydrazone of Cyclohexanone.



The hydrochloride of 2:3-dimethylphenylhydrazine (0.5g) was mixed with cyclohexanone (0.28g) and sodium acetate and boiled gently for 30 minutes. The liquid was filtered to remove sodium chloride and diluted with water, when an oil separated. This could not be induced to crystallise either by trituration or crystallisation from the usual solvents.

Attempted synthesis of 7:8-Dimethyltetrahydrocarbazole by the method of Rogers and Corson (J.A.C.S., 1947, 69, 2910).



The hydrochloride of 2:3-dimethylphenylhydrazine (0.54g), 75% ethyl alcohol (4.6 ml.) and hydrochloric acid (0.8 ml.) were boiled under reflux with stirring, while 0.5g cyclohexanone was added gradually/

gradually over a period of one hour. The liquid was boiled for a further hour, and cooled, but no solid separated on standing. Treatment with water precipitated a brown solid which was extracted with ether, and the ether extract dried over anhydrous sodium sulphate, and evaporated. A brown oil was left which partly solidified on standing. Some of the colourless solid which separated was washed with a little benzene. It melted with decomposition at 109°C, and its solution in alcohol gave a bright green fluorescence. A mixed melting-point with 2:3-dimethylphenylhydrazine showed a considerable depression. The compound, very slightly soluble in light petroleum to give a bright green fluorescence, appeared similar to that obtained during attempted crystallisation of 7:8-dimethyltetrahydrocarbazole from light petroleum. The oil did not yield a solid either by trituration with or attempted crystallisation from light petroleum, benzene or alcohol. Formation of a picrate was attempted in benzene solution, and although the solution immediately became dark chocolate-brown in colour, no picrate could be induced to crystallise.

Attempted/

Attempted preparation of 6:8-Dimethyltetrahydrocarbazole (Rogers and Corson)

2:4-Dimethylphenylhydrazine (2.16g) prepared by the method of Willgerodt and Klein (J. Prakt. Chem. 1899 [2] 60, 102), and decomposing slightly, was heated under reflux with hydrochloric acid and 75% ethyl alcohol, while cyclohexanone was added gradually. The final product was obtained as a brown oil which could not be induced to crystallise. Formation of a picrate was attempted without success in benzene solution.

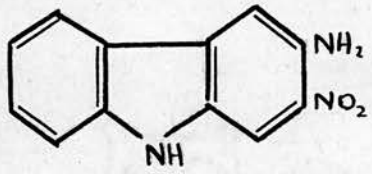
The experiment was repeated using the 'organic acid' method of Rogers and Corson. The dimethylphenylhydrazine (2.16g) was added during one hour to a boiling mixture of cyclohexanone (1.96g) and 7.2g glacial acetic acid. The liquid was boiled for a further hour and cooled thoroughly. No solid separated. Dilution with water precipitated a brown tar which was extracted with ether. The extract was dried (anhydrous sodium sulphate) and evaporated, leaving a brown oil which did not crystallise or form a picrate. Attempted crystallisation from, and trituration with, benzene, light petroleum, alcohol and aqueous alcohol did not yield a solid.

No further attempts were made to prepare dimethyltetrahydrocarbazoles by the Borsche method.

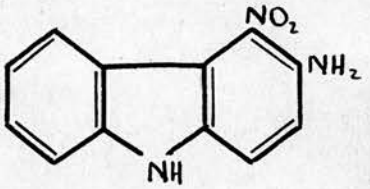
DISCUSSION OF EXPERIMENTAL RESULTS.

In 1928 Kehrmann prepared 2-nitro-3-aminocarbazole and 4-nitro-3-aminocarbazole, but did not orientate them (44). Some years later the conversion of these compounds to 2-nitro- and 4-nitrocarbazole by the elimination of the amino groups was reported in a British patent (43). As already shown in the introduction, sufficient evidence was not given to distinguish and identify the nitrocarbazoles obtained.

In the course of this research the work of Kehrmann has been repeated, with certain modifications to give greater yields or cleaner products, and two isomeric nitrocarbazoles have been obtained from the resulting amines by the method described in the patent. Authentic samples of 2- and 4-nitrocarbazole were prepared by the dehydrogenation of 7- and 5-nitrotetrahydrocarbazole, and compared, by melting-point and mixed melting-point, with the two unknown nitrocarbazoles. It has been shown beyond doubt that the claims of the patent are justified. α- and β-nitro-3-aminocarbazole yield on de-amination 2- and 4-nitrocarbazole respectively, proving that α-nitro-3-aminocarbazole has a nitro group in the 2-position; β- in the 4-position:-



α-NITRO-3-AMINOCARBAZOLE



β-NITRO-3-AMINOCARBAZOLE

2-Nitrocarbazole was obtained as pure yellow needles or prisms from benzene, melting at 173°C (cf p. 14), and 4-nitrocarbazole as orange compact prisms, m.p. 179/80°C.

This method of preparing 2- and 4-nitrocarbazoles by substitution is very tedious and gives poor yields, in no way comparable to those obtained by synthesis. In the reduction of 3-nitrocarbazole with tin and hydrochloric acid (p. 28) a tin double salt was obtained, but treatment of this for half-an-hour (lit.) with acetic anhydride and anhydrous sodium acetate gave only a minute yield of 3-acetamidocarbazole. A reaction time of at least 6 hours was necessary to give optimum yields. The final product was highly contaminated with a dark green oily material which could only be removed by repeated crystallisation, thus considerably reducing the yield. The use of analar stannous chloride in the reduction did not alleviate this difficulty. The highest yield obtained in several attempts was 25%, but by the method of Whitner (46) a 40% yield of the pure 3-acetamidocarbazole was obtained in a much shorter time. Further acetylation to give a mixture of di- and triacetyl-3-aminocarbazole was/

was most conveniently accomplished by boiling with acetic anhydride and a trace of sulphuric acid, which gave a good yield. After nitration an attempt was made to separate 2- and 4-nitro-3-diacetamidocarbazole by chromatographic adsorption. A separation was not obtained, but a partial hydrolysis of the 2-nitro-isomer occurred giving bright red 2-nitro-3-acetamidocarbazole. Similar hydrolysis of the 4-isomer did not appear to occur. The red colour was strongest on the circumference of the chromatogram, with a gradation inwards until in the centre the colour was pure yellow, suggesting that the hydrolysis was accomplished by the action of alumina in the presence of light. No trace of a red colour was noticed for the first 24 hours, and the quantity of 2-nitro-3-acetamidocarbazole isolated after 3 days was very small. The preparation of alumina for use in chromatography results in slight contamination of the final product with alkali. This fact, together with the basic nature of alumina and the finely divided condition in which it is employed in chromatographic adsorption, probably accounts for the hydrolytic action. In a later experiment (p. 37) a small quantity of the diacetamido isomers passed through a column unchanged within 8 hours. By the partial hydrolysis of a

mixture/

mixture of 2- and 4-nitro-3-diacetamidocarbazole with alcoholic sodium hydroxide, 2-nitro-3-acetamidocarbazole, which is not very soluble in alcohol, was easily isolated and subsequently converted to the amine in a straightforward manner by acid hydrolysis. Difficulties were encountered during the isolation of the 4-isomer, however. Treatment of the diacetamido-isomers with alkali must not be carried out for too long or further hydrolysis will occur giving 2- (and possibly 4-) nitro-3-aminocarbazole, which cannot readily be separated from 4-nitro-3-acetamidocarbazole. The best results were obtained by treatment for 15 minutes, although a little 4-nitro-3-diacetamidocarbazole, which does not appear to have been separated before, was isolated. In that time, 2-nitro-3-diacetamidocarbazole had been completely converted to the corresponding monoacetyl derivative, but further hydrolysis to the amine had not occurred. This experiment, in conjunction with the hydrolysis by alumina of 2- and not 4-nitro-3-diacetamidocarbazole, shows that the latter is more stable to alkaline hydrolysis than is the former. Acid hydrolysis of 4-nitro-3-acetamidocarbazole did not produce such a clean product as the 2-isomer, but recrystallisation from alcohol yielded pure 4-nitro-3-aminocarbazole.

2-Aminocarbazole/

2-Aminocarbazole

The claim in British Patent 340,550 that the removal of the amino-group from α-nitro-3-aminocarbazole gives 2-nitrocarbazole has now been confirmed, and there is little doubt that reduction of the product with tin and hydrochloric acid yielded 2-aminocarbazole, m.p. 238°C, as described. No details of procedure or analysis figures were included, however, and although the product was said to be identical with that of Blank (37), no direct mixed melting-point comparison was reported, and Blank's work had several unsatisfactory features (see p. 13). It was therefore considered of value to carry out a catalytic reduction of 2-nitrocarbazole in order to obtain 2-aminocarbazole, and compare it directly with the product obtained by a method similar to Blank's, i.e., by pyrolysis of 2:4'-diaminodiphenyl.

The reduction apparatus was standarised by reducing $\frac{1}{100}$ mol benzoin in alcoholic solution. α-Nitronaphthalene and 3-nitrocarbazole were also successfully reduced, thus showing the applicability of the method to nitro-compounds and, in particular, to a nitrocarbazole. During the reduction of 2-nitrocarbazole a quantity of hydrogen was absorbed sufficient to effect the change $-NO_2 \rightarrow NH_2$, and a sample of pure 2-aminocarbazole, m.p. 238/9°C, which/

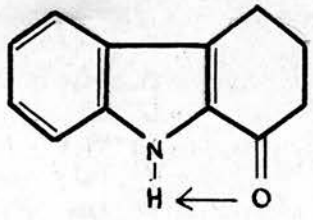
which was obtained in 25% yield, was analysed. Comparison with the product obtained by the pyrolysis of an oil assumed to consist mainly of 2:4'-diaminodiphenyl (since the theoretical quantity of hydrogen was absorbed in the reduction of 2:4'-dinitrodiphenyl) showed that in this case also 2-aminocarbazole was formed, confirming Blank's experiment of 1891.

4-Aminocarbazole.

A similar catalytic reduction of 4-nitrocarbazole did not lead to the isolation of pure 4-aminocarbazole, but by the action of acetyl chloride on an alcoholic solution of the crude solid a product assumed to be 4-acetamidocarbazole was obtained in very small yield.

Attempted preparation of 1-substituted methyl carbazoles from derivatives of 1-keto-1:2:3:4-tetrahydrocarbazole.

The preparation of 1-methyl carbazole by the action of methyl magnesium iodide on 1-keto-tetrahydrocarbazole does not seem possible, several attempts in both ether and anisole solution proving unsuccessful (p. 55). Even when a reaction period of 24 hours was allowed, unchanged ketotetrahydrocarbazole was obtained. It seems, therefore, that the keto-group is not so reactive as might be expected, although Coffey found (53) that a ketazine and a semicarbazide could be formed. He also noted that the imino-group was much less reactive than in tetrahydrocarbazole and did not undergo acetylation or benzoylation. This fact in conjunction with the apparent lack of activity of the keto-group towards methyl magnesium iodide suggests the formation of a chelate ring:-



To break such a ring the N-methyl derivatives of 1-ketotetrahydrocarbazole and 7:8-dimethylketotetrahydrocarbazole were prepared. These compounds failed/

failed to react with methyl magnesium iodide, however, and this lack of reactivity cannot be attributed to chelation. A chelate ring may exist in ketotetrahydrocarbazole, but if so it does not fully explain its failure to react with methyl magnesium iodide.

Further attempts to prepare 1-methylcarbazole derivatives by this method were not made.

Preparation of Dimethyl-derivatives of 1-Ketotetrahydrocarbazole and Carbazole.

By the condensation of oxymethylene cyclohexanone with various diazotised xylidines, and treatment of the resulting dimethylphenylhydrazones of cyclohexane-1:2-dione with glacial acetic and hydrochloric acids, dimethyl derivatives of ketotetrahydrocarbazole have been prepared and reduced to dimethyltetrahydrocarbazoles. The method is characterised by the very clean condition in which the reaction products are obtained in the first and final stages, i.e., the preparation of the hydrazones and reduction of the ketones, but in most cases the latter were contaminated with a brown impurity which was easily removed by recrystallisation from benzene (charcoal), or chromatographic adsorption. Dimethylketotetrahydrocarbazoles are/

are colourless or pale amber stable solids, only slightly soluble in light petroleum, but in most cases very soluble in benzene and hot glacial acetic acid. In every case but one Clemmensen reduction gave very good yields of the corresponding crystalline dimethyltetrahydrocarbazoles, none of which has been described in the literature. The efficiency of the method was previously tested by reduction of ketotetrahydrocarbazole and 8-methylketotetrahydrocarbazole, giving tetrahydrocarbazole (55% yield) and 8-methyltetrahydrocarbazole (87% yield), which were compared with authentic samples prepared by the Borsche synthesis.

Those dimethylphenylhydrazones of cyclohexane-1:2-dione which have been prepared are deeply coloured highly crystalline stable solids which do not show any signs of decomposition on long exposure to light and air. Their preparation does not involve the isolation of dimethylphenylhydrazines, most of which are unstable substances decomposing in light and air to brown oily materials, but they are instead prepared in a one-stage process from the corresponding xylidines. Attempts to prepare 7:8- and 6:8-dimethyltetrahydrocarbazole by the Borsche synthesis from 2:3- and 2:4-dimethylphenylhydrazine were unsuccessful, although the former phenylhydrazine was fairly stable.

The total number of stages in this synthesis, from amine to tetrahydrocarbazole, is of course the same as in the Borsche synthesis, and one more than the modification of Rogers and Corson, since reduction is necessary, but this is accomplished in good yield and the resulting tetrahydrocarbazoles thus obtained are only very slightly impure.

By dehydrogenation with chloranil in xylene solution the dimethyltetrahydrocarbazoles yielded dimethylcarbazoles, several of which had not before been described. Ullmann (17) described the synthesis of 1:3-dimethylcarbazole by the distillation of the corresponding benztriazole carboxylic acid over quicklime. The oily distillate contained 2-methylacridine in addition to the carbazole, whose yield was not quoted. 2:4-dimethylcarbazole has been prepared in very good yield by dehydrogenation of 2:4-dimethyl-1:2:3:4-tetrahydrocarbazole with 5% Pd/C catalyst (28) The tetrahydrocarbazole was prepared by Rogers and Corson (29). 1:2-, 1:3-, 1:4-, 2:3- and 3:4-dimethylcarbazoles have now been prepared from the corresponding tetrahydrocarbazoles so that no dimethylcarbazole with both methyl groups in the same aromatic ring remains to be described. Of the dimethylcarbazoles described, only two gave the deep/

deep blue green colour, characteristic of many carbazole derivatives, on treatment with sulphuric acid and a drop of nitric acid. Their solution in benzene or light petroleum exhibited a bright blue fluorescence which was not removed by chromatographic adsorption.

The cyclisation of the Mono-3:4-dimethylphenylhydrazone of Cyclohexane-1:2-dione, (p. 79)

When this hydrazone is cyclised two dimethylketotetrahydrocarbazoles may, in theory, be formed, and in practice this was found to be so. A separation was accomplished by a laborious combination of fractional extraction with ether, chromatographic adsorption and mechanical means into two ketones, m.p. 201°C and 225/7°C. Although several products were obtained melting over only two or three degrees between 170°C and 180°C, these were shown to be mixtures. The sharpness of the melting-point tended to suggest the formation of a molecular compound, but if this were so, products melting a good deal lower might also be expected (compound AB contaminated with A or B thus depressing the melting-point), and none was found.

Reduction of the dimethylketotetrahydrocarbazole, m.p. 201°C, did not give a tetrahydrocarbazole with a sharp melting-point, but a picrate of/

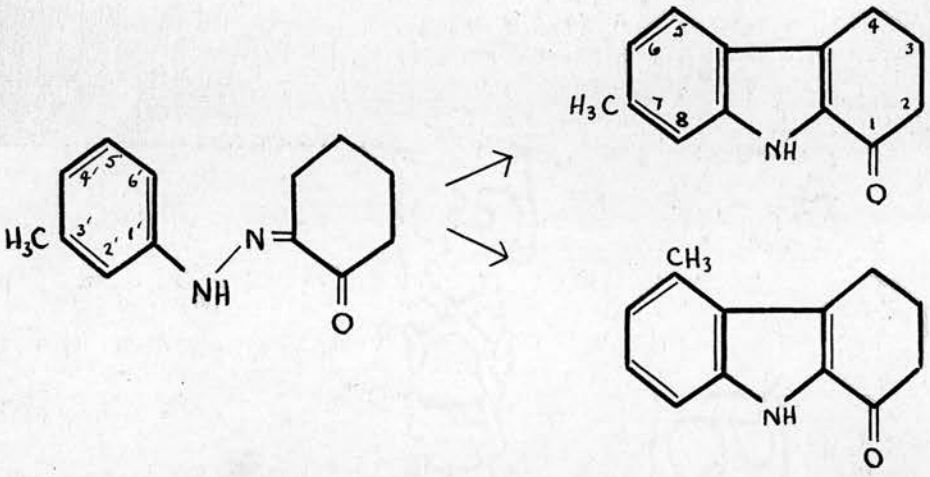
of the latter substance melted very sharply, and dehydrogenation gave a 42% yield of a single dimethylcarbazole, m.p. 250/2°C (in the majority of cases chloranil dehydrogenation of dimethyltetrahydrocarbazoles was found to give yields of between 40% and 50%). The wide melting-range of the tetrahydrocarbazole was thus, in all probability, caused by the presence of only a trace of impurity not readily removed by recrystallisation from light petroleum. The other ketone, m.p. 225/7°C, yielded an oil on reduction, but dehydrogenation gave a 43% yield of a product which was later shown to be 3:4-dimethylcarbazole (p. 86), proving that the oil consisted mainly of 5:6-dimethyltetrahydrocarbazole. Thus 2:3-dimethylcarbazole has a melting-point of 250/2°C, and 5:6- and 6:7-dimethylketotetrahydrocarbazole melt at 225/7°C and 201°C respectively. (The method of orientation of these compounds will now be dealt with completely).

Orientation of the two Dimethylketotetrahydrocarbazoles prepared by cyclisation of the Mono-3:4-Dimethylphenylhydrazone of Cyclohexanone-1:2-dione, (p. 87)

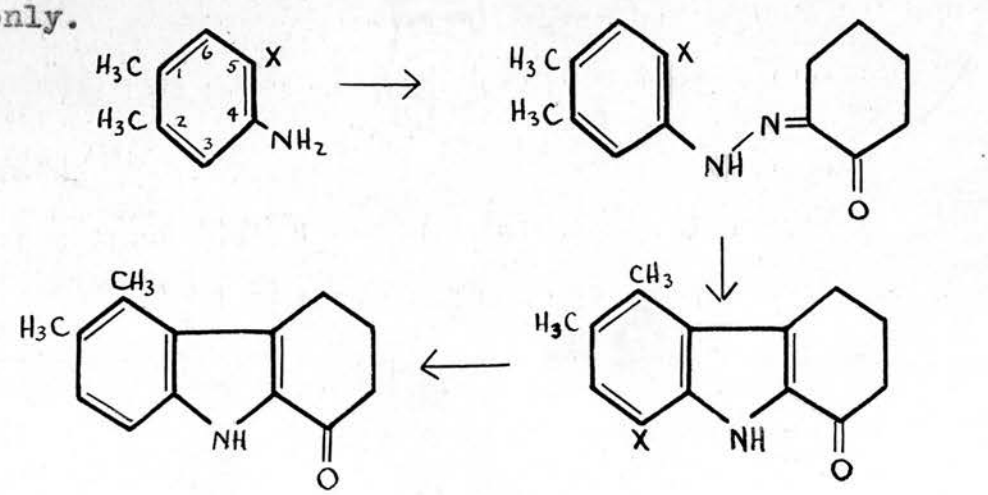
Kent has shown (60) that when the mono-m-tolylhydrazone of cyclohexane-1:2-dione is boiled with glacial acetic and hydrochloric acids, both

5-/

5- and 7-methylketotetrahydrocarbazole are formed.



Similarly, as already mentioned, the 3:4-dimethylphenylhydrazone yielded both 5:6- and 6:7-dimethylketotetrahydrocarbazole, which were separated, reduced and dehydrogenated to two isomeric dimethylcarbazoles. An orientation of the ketones, or the carbazoles, was desirable. To do this it was decided to apply Coffey's synthesis to o-4-xylidine containing an easily removable substituent in the 3- or 5-positions (equivalent to 2'- or 6'-above) so that cyclisation could occur in one way only.

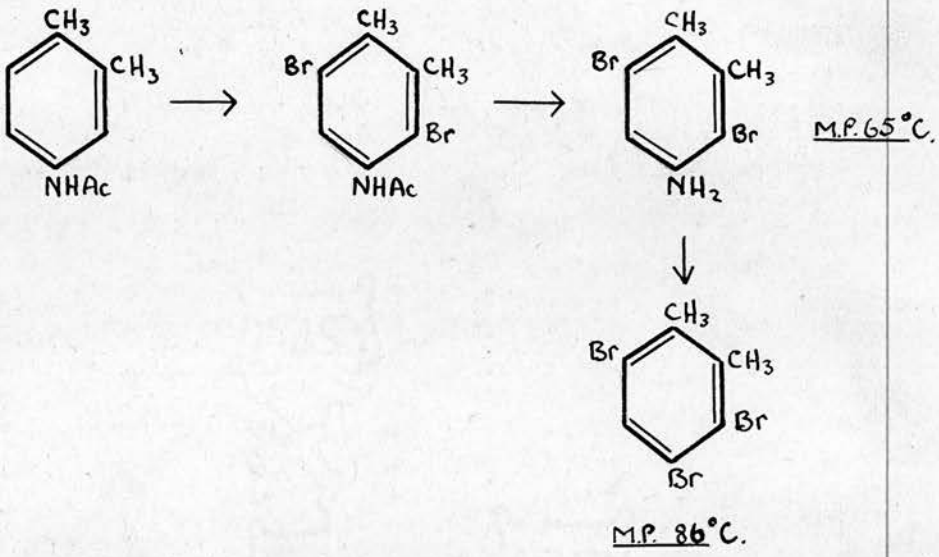


Such a compound described in the literature was 3:6-dibromo-o-4-xylidine, stated by Jaeger and Blanksma (62) to be prepared by bromination of acetyl-o-4-xylidine and subsequent hydrolysis. Although it seemed unusual that substitution should take place in the 6- rather than the 5- position, attempts were made to prepare the compound, but even when excess bromine was added and heat applied only a monobromo-acetyl-xylidine was isolated, m.p. 165/6°C, which appeared to correspond to a compound described by Mills and Nixon (63) namely acetyl-5-bromo-o-4-xylidine, m.p. 164°C.

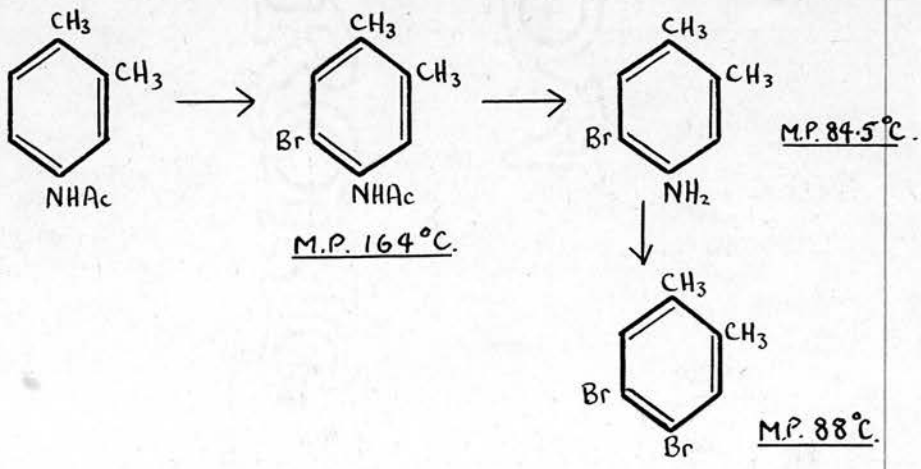
Furthermore, accounts given of the bromination of acetyl-o-4-xylidine in glacial acetic acid solution by Mills and Nixon on the one hand, and Jaeger and Blanksma on the other, are obviously incompatible.

According to Jaeger and Blanksma, the product obtained on treatment with 2-moles of bromine was acetyl-3:6-dibromo-o-4-xylidine, but no melting-point was quoted. Hydrolysis with caustic soda yielded 3:6-dibromo-o-4-xylidine, m.p. 65°C. A 'Sandmeyer' reaction gave 3:4:6-tribromo-1:2-dimethylbenzene, m.p. 86°C. No analysis figures were included/

included at any stage.

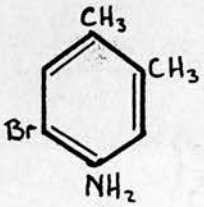


Mills and Nixon contended that bromination with 1 mol bromine yielded acetyl-5-bromo-o-4-xylidine, m.p. 164°C, hydrolysis gave the amine, m.p. 84.5°C, and the latter, by the 'Sandmeyer' reaction gave 4:5-dibromo-1:2-dimethylbenzene, m.p. 88°C. Analysis figures were included at each stage, together with full experimental details.

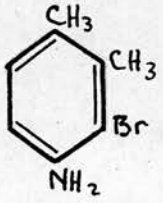


In this research it has been found (p. 87) that treatment of acetyl-o-4-xylidine in acetic acid solution with more than 2 moles of bromine yields/

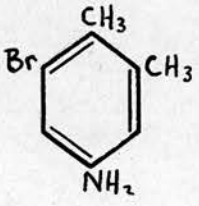
yields a monobromo derivative, m.p. 165/6°C. Hydrolysis gives an amine, m.p. 85/7°C, which must have the structure A, B. or C.



A



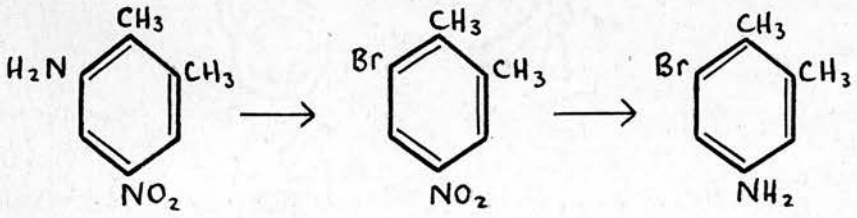
B



C

Since the amino- or acetamido-group has a strong o-directive influence, and the 5-position is less sterically hindered than the 3-position, the most probable structure would seem to be A.

The compound C has been prepared by Crossley and Bartlett (64) by a method which leaves no doubt as to the structure; 5-nitro-o-3-xylidine, whose structure has been proved, by a 'Sandmeyer' reaction and subsequent reduction yields 6-bromo-o-4-xylidine, m.p. 82°C. The acetyl and diacetyl derivatives melt at 205/6°C and 109°C respectively.



Structure C can thus be eliminated.

A 'Sandmeyer' reaction on the monobromo-o-4-xylidine was found by Mills and Nixon to give

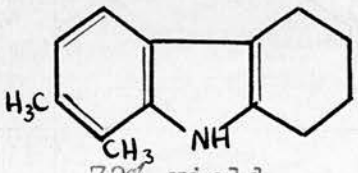
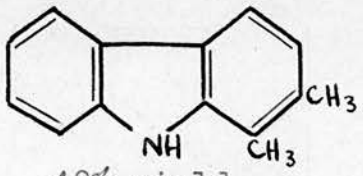
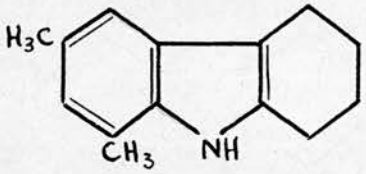
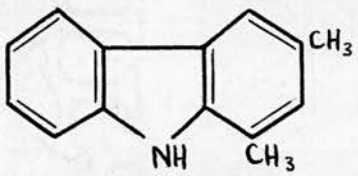
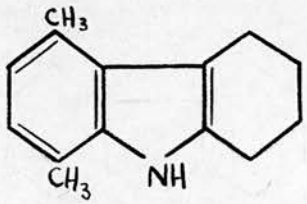
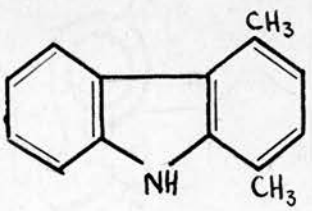
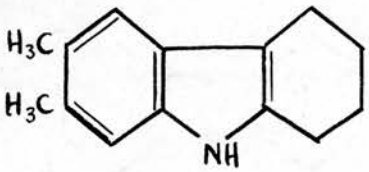
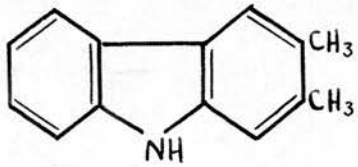
a/

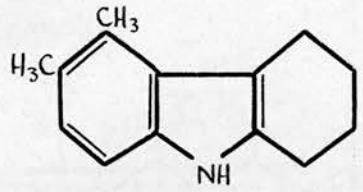
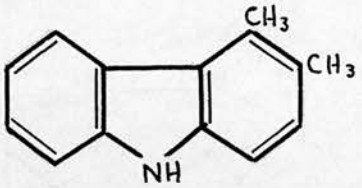
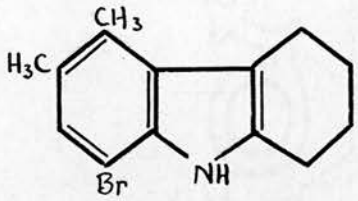
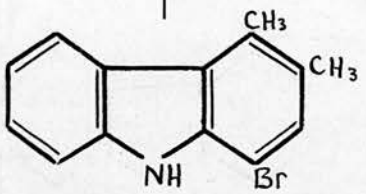
a substance, m.p. 88°C, which must be a dibromodimethylbenzene (analysis confirmed this), either 3:4- or 4:5-dibromo-1:2-dimethylbenzene. The latter, m.p. 88°C, was prepared by Jacobsen (65) who proved its constitution by conversion to 1:2:4:5-tetramethylbenzene (durene) by treatment with methyl iodide and sodium. 3:4-Dibromo-1:2-dimethylbenzene appears to be a liquid at ordinary temperatures, crystallising to form a solid melting at 7°C (65, 66).

Thus when acetyl-o-4-xylidine is brominated in glacial acetic acid solution, acetyl-5-bromo-o-4-xylidine is formed. This compound is also a suitable starting material for the orientation of 5:6- and 6:7-dimethylketotetrahydrocarbazoles since the 5-position is blocked and synthesis of 8-bromo-5:6-dimethylketotetrahydrocarbazole was accomplished. Debromination of the corresponding tetrahydrocarbazole with Raney nickel did not succeed, but after conversion to the carbazole the bromine was successfully removed by the action of hydriodic acid and red phosphorus, giving 3:4-dimethylcarbazole. A direct comparison was then made with the isomeric dimethylcarbazoles obtained by reduction and dehydrogenation of the original ketotetrahydrocarbazoles.

List/

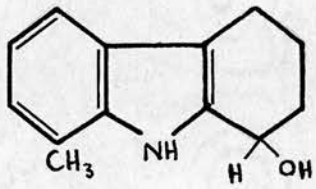
List of Dimethyltetrahydrocarbazoles and Dimethylcarbazoles prepared.

Dimethyltetrahydrocarbazole. Yield and melting-point of product obtained by Clemmensen reduction of the corresponding dimethyl-1-ketotetrahydrocarbazole.	Page No.	Dimethylcarbazole. Yield and melting-point of product obtained by chloranil dehydrogenation of the corresponding dimethyltetrahydrocarbazole.	Page No.
 72% yield before recrystallisation m.p. 84/6°C.	65	 42% yield m.p. 147/8°C	68
 72% yield m.p. 92/94°C	76	 26% yield m.p. 94°C (Lit. 95°C)	77
 98% yield m.p. 88/9°C	71	 52% yield m.p. 79/82°C	73
 78% yield m.p. 119/130°C	83	 42% yield m.p. 250/2°C.	84

	Page No.		Page No.
	85		86
This was obtained as an oil which could not be crystallised.		43% yield m.p. 159/60°C	
		↑	
	90		92
74% yield m.p. 101°C.		50% yield m.p. 98/9°C.	

The isolation of unidentified products during the purification of some alkyl tetrahydrocarbazoles.

On the reduction of 8-methyltetrahydrocarbazole with zinc amalgam and hydrochloric acid a product was obtained which was recrystallised from light petroleum to give a colourless solid melting with decomposition at 122°C. Since authentic 8-methyltetrahydrocarbazole melts at 97/8°C, with no decomposition, it was at first assumed that reduction had not proceeded completely, and that 8-methyl-1-hydroxytetrahydrocarbazole had been formed, but analysis of the compound disproved this.



$C_{13}H_{15}ON$	Requires	Found
% Carbon	77.61	72.63
% Hydrogen	7.46	7.46

Neither did it seem that simple addition of water had taken place.

$C_{13}H_{15}N.\ H_2O$ Requires C, 76.85%; H, 8.37%

$C_{13}H_{15}N.\ 2H_2O$ " " 70.58% " 8.60%

This substance was not investigated further, nor was it analysed again, but the empirical formula was probably $C_{13}H_{15}O_2N$

$C_{13}H_{15}O_2N$ Requires C 71.88%; H 6.91%

Repetition of the reduction under apparently similar conditions gave, on recrystallisation from aqueous alcohol, an 87% yield of the required 8-methyltetrahydrocarbazole.

Similar compounds were isolated in the case of some dimethyltetrahydrocarbazoles. For example 7:8-dimethylketotetrahydrocarbazole on reduction gave a crude crystalline solid, m.p. 80/2°C, three portions of which were crystallised separately from light petroleum giving in two cases amorphous solids melting with decomposition at 106/7°C and 115°C, and in the third a crystalline solid, m.p. 84/6°C. The analyses of these compounds were as follows:

	Crude Solid (m.p. 80/82°C)	A (m.p. 106/7°C)(d)	B (m.p. 115°C)(d)	C (m.p. 84/6°C
% C	82.41	72.83	72.23	83.89
% H	8.31	7.23	7.27	8.81
% N			7.46	7.23

$C_{14}H_{17}N$ requires C, 84.41%; H, 8.54%; N, 7.03%

$C_{14}H_{17}NO_2$ " C, 72.73%; H, 7.36%; N, 6.06%

The last compound, C, was obviously 7:8-dimethyltetrahydrocarbazole, and formed a chocolate/

chocolate-brown picrate, characteristic of methyltetrahydrocarbazoles. It was obvious too that the crude reaction product, m.p. 80/2°C, was not a simple mixture. In the first place its analysis and melting-point seemed to show that it consisted mainly of the required tetrahydrocarbazole, and it formed a chocolate-brown picrate with a fairly sharp melting-point, corresponding to that prepared from the pure substance. In addition, although the third crystallisation yielded mainly the pure tetrahydrocarbazole (a little of the substance m.p. 115°C (d) was isolated from the mother-liquor), the only product obtained from the second recrystallisation was the higher melting solid B.

5:8- and 6:8-dimethyltetrahydrocarbazole gave similar compounds, m.p. 128°C and 130°C, with decomposition, but these were not analysed. McCall (36) who has since prepared 5:8- and 6:8-dimethyltetrahydrocarbazoles by condensation of o-chlorocyclohexanone with the appropriate xylidines (p. 9) isolated compounds during their recrystallisation, which analysed as follows:

From 5:8-dimethyltetrahydrocarbazole -

Found C, 72.66%; H, 7.46%; N, 6.10%

From 6:8-dimethyltetrahydrocarbazole -

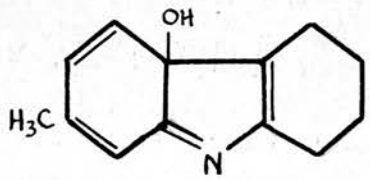
Found C, 73.70%; H, 7.71%; N, 5.90%

These/

These substances would not form picrates.

It is therefore clear that these colourless substances are not formed during the reduction of ketotetrahydrocarbazoles, but are produced from the actual tetrahydrocarbazoles in solution. A solution of these pure dimethyltetrahydrocarbazoles in ether, alcohol, benzene or light petroleum at first shows no fluorescence, but soon a green fluorescence appears, becoming very strong in a matter of hours. The solubility in benzene and light petroleum of the substances is much less than that of the corresponding tetrahydrocarbazoles, for when a sample of the latter is dissolved in the minimum of benzene or light petroleum, the solid which separates slowly will not redissolve in several times the amount of solvent originally used.

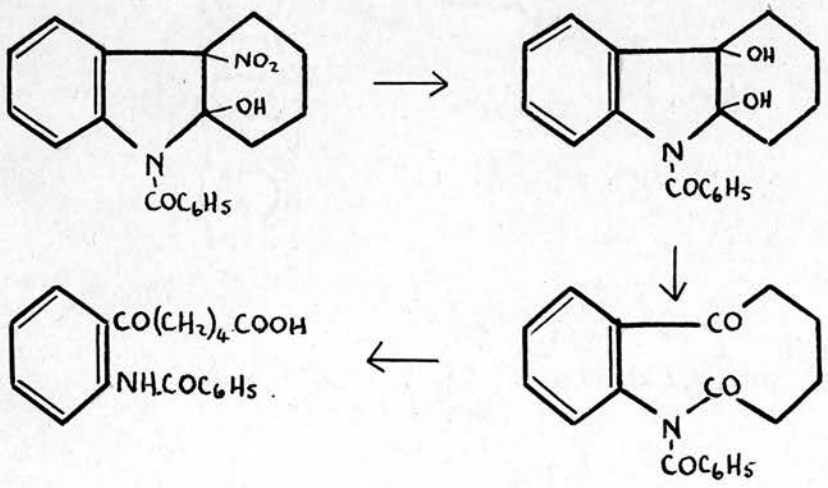
Pausacker and Robinson (67) during the preparation of 8-chloro-5-methyltetrahydrocarbazole by the action of dilute sulphuric acid on the 2-chloro-5-methylphenylhydrazone of cyclohexanone, isolated a product to which they assigned the structure:-



This/

This, produced in small quantity together with a good yield of the required tetrahydrocarbazole, they named 12-hydroxy-7-methyl-1:2:3:4-tetrahydroisocarbazole. The compound appears to have been formed during the actual cyclisation, however, and the tetrahydrocarbazoles obtained in this research were prepared by reduction of pure ketotetrahydrocarbazoles.

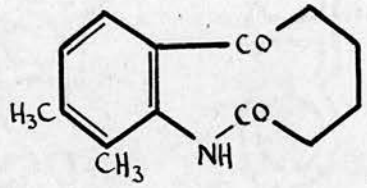
Perkin and Plant (25) found that if 11-nitro-9-benzoyl-10-hydroxyhexahydrocarbazole, prepared by the action of nitric acid on 9-benzoyltetrahydrocarbazole (p. 18), is boiled with aqueous alcoholic caustic potash, two acids are formed. The main product is δ -(o-benzoylaminobenzoyl) valeric acid, together with a little δ -o-aminobenzoylvaleric acid, and they supposed the following series of reactions took place:-



The/

The action of alkali hydrolised the nitro-group to hydroxyl; the two hydroxyl groups were then oxidised by nitrite to a diketone which on further hydrolysis with alkali yielded the final acids.

Now the compounds obtained on prolonged solution of dimethyltetrahydrocarbazoles have the empirical formula $C_{14}H_{17}O_2N$, suggesting simple oxidation of the parent tetrahydrocarbazole. Since the 10:11-double bond in tetrahydrocarbazoles is very reactive, it is possible that they are of the type:-



No conclusive evidence of this has been found, however, and the structure of those compounds obtained during the attempted purification of dimethyltetrahydrocarbazoles must remain open to conjecture.

ADDENDUM.

A note has recently been published in 'Nature' (1949, 164, 362), in which is postulated the formation of peroxides by aerial oxidation of tetrahydrocarbazoles.

very/

very soluble in the cold. Here one further advantage of the preparation of dimethyltetrahydrocarbazoles by reduction of the corresponding ketotetrahydrocarbazoles becomes evident. The latter are easily obtained in a pure state by crystallisation; apparently possessing none of this activity with regard to oxidation, and Clemmensen reduction gives high yields of the tetrahydrocarbazoles in a very clean condition. One rapid recrystallisation from the minimum of light petroleum of suitable boiling point yields the pure substance. The same tetrahydrocarbazoles prepared by condensation of cyclohexanone and dimethylphenylhydrazines, with cyclisation of the corresponding hydrazones, would probably be obtained with much impurity, and isolation would be difficult. One instance of this was noted in the attempted preparation of 7:8-dimethyltetrahydrocarbazole by the method of Rogers and Corson. The oil which was obtained could not be induced to yield the required tetrahydrocarbazole, although an attempt to form a picrate gave the usual chocolate-brown colour, suggesting that the tetrahydrocarbazole was present. Furthermore, a colourless solid was isolated, corresponding to that obtained by boiling a solution of 7:8-dimethyltetrahydrocarbazole in light petroleum.

In/

In conclusion it would seem that Coffey's synthesis provides a very good method of preparing certain alkyl tetrahydrocarbazoles which would be difficult, if not impossible, to prepare by the Borsche synthesis.

SUMMARY.

An orientation has been carried out of 2- and 4-nitro-3-aminocarbazole by an examination of the products obtained on de-amination.

2-Aminocarbazole has been prepared by reduction of 2-nitrocarbazole and by pyrolysis of 2:4'-diaminodiphenyl. Isolation of 4-aminocarbazole by reduction of 4-nitrocarbazole was not achieved, but the acetyl derivative was obtained.

Attempts to prepare 1-substituted methyl carbazoles by the action of methyl magnesium iodide on ketotetrahydrocarbazole and two of its derivatives were not successful.

Extension of Coffey's synthesis proved advantageous in the preparation of dimethyltetrahydrocarbazoles from which were obtained the corresponding carbazoles.

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65	Jacobsen	Ber. 1884, 17, 2376
66	Coffey	Rec. Trav. Chim. 1923, 42, 433
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POSTSCRIPT.

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